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AN EARLY HUMAN EMBRYO (No. 1285, MANCHESTER COLLECTION), WITH CAPSULAR ATTACHMENT OF THE CONNECTING STALK

By J. FLORIAN, M.D. and J. P. HILL, D.Sc., F.R.S.

From the Department of Anatomy and Embryology, University College, London

The specimen described herein (No. 1285 of the collection of the Department of Anatomy, University of Manchester) was placed at our disposal by Prof. J. S. B. Stopford, F.R.S., and to him we desire to express our very grateful thanks for his generous action.

In our paper (1931) on the Dobbin embryo, we included, for comparative purposes, an account of the head-process and prochordal plate of this embryo and provided a graphic reconstruction of the dorsal view of the embryonal shield (1931, text-fig. 5), and although its state of preservation is not perfect, we think the chorionic vesicle as a whole is well deserving of brief description, since it exhibits certain features of unique interest.

HISTORY OF THE SPECIMEN

Prof. Stopford informs us that he received the pregnant uterus (which provided the specimen) from his colleague, Prof. Daniel Dougal, M.C., M.D., some few hours after its removal. Unfortunately it is not now possible to obtain the full history of the case, but Prof. Dougal, although he did not himself perform the operation, has very kindly given us such information as he possesses concerning it. The uterus was removed by hysterectomy, following on chronic metritis. From the notes taken by the house-surgeon, pregnancy was not suspected, and the operation was undertaken by one of Prof. Dougal's colleagues. When the uterus was exposed, its appearance suggested to him the possibility of an early pregnancy. Some hours after the completion of the operation, Prof. Dougal had occasion to examine the uterus, and recognising its value, took it immediately to Prof. Stopford.

On looking more carefully into the record of the menstrual history of the patient, Prof. Dougal found that she had a normal periodicity of about 21 days and that the actual time intervening between the last menstrual period and the date of operation was 28 days, so that she had actually overrun a missed menstrual period by about a week.

If we assume that fertilisation occurred at mid-interval, say on the 11th day of the cycle, and that the 28 days' interval is reckoned from the onset of

menstruation, the fertilisation-age of the present specimen would be 17 days, which we think is too low, but the available data are not exact enough for an accurate determination.

The specimen, comprising the completely implanted chorionic vesicle with the embryonal primordium and the immediately surrounding portion of the decidua, came into our hands as a very fine, complete series of sections which had been cut at a uniform thickness of 8 μ. We have numbered the sections containing the embryo and those immediately adjoining the latter in serial cranio-caudal order from 1 to 160. The embryo has been cut in a very favourable plane for study; the sections are nearly transverse to the embryonic axis (the difference between the sectional plane and the transverse plane being 9° 30′ as can be seen from our reconstruction of the dorsal view (text-fig. 1)) and are practically perpendicular to the plane of the embryonal shield. As our graphic reconstruction of the median section (text-fig. 2) shows, the outline of the embryo (especially that of the ventral wall of the yolk-sac and the chorionic ectoderm) is very uneven. This is due to variations in the dorso-ventral dimensions of the sections, the result of unequal expansion. The specimen, moreover, exhibits distinct signs of shrinkage of the embryonal vesicles, as the result of which the embryonal ectoderm has become largely detached from the underlying layers. This detachment is most marked in the cranial part of the embryonal shield and in the region of the cloacal membrane, the caudal part of which has become artificially separated into its constituent layers. Likewise the allantoic canal has been broken across and separated into two portions. In view of these defects, we have thought it advisable to provide, along with the accurate graphic reconstruction of the median section (text-fig. 2), an idealised figure of the same in which obvious imperfections have been corrected (text-fig. 3).

MEASUREMENTS

Chorionic vesicle including villi = implantation cavity: polar diameter 5 mm.; maximum transverse diameter 4·4 mm.

Chorionic cavity without villi = exocoelom: polar diameter 4·28 mm.; transverse diameter 3·28 mm. (The foregoing measurements relate to section 160.)

Amniotic cavity: length 0·91 mm.; height 0·23 mm.

Embryonal shield, including cloacal membrane: length 0·87 mm. (text-fig. 2); breadth 0·625 mm. (text-fig. 1).

Cloacal membrane: length 0·06 mm.

Primitive streak: length 0·39 mm.

Hensen's knot: length 0·05 mm.

Head-process: length 0·125 mm.

Prochordal plate: length 0·03 mm.

Yolk-sac cavity (text-fig. 2): Cr.-Cd. diameter (length) 0·98 mm., vertical diameter (height) 0·74 mm., transverse diameter 0·988 mm. (in section 80).

Allantoic canal: length (allowing for break), 0·23 mm.; thickness of bulbous upper end 0·04 mm.

The chorionic vesicle of pear-shaped outline in section (Plate III, fig. 11) is implanted in the decidua immediately to the left of a deep groove, the lower part of the decidua capsularis and the decidua marginalis actually forming the boundary of the groove on its side next the vesicle. From the figure, it will be seen that the embryo is attached to the chorion, not at the deep pole of the vesicle as is normally the case, but at its superficial pole, underlying the capsularis. This is unquestionably the most interesting feature displayed by the present specimen. It had already been noted by Prof. Stopford, and, so far as we are aware, the present specimen appears to be the only early human embryo in which this condition has actually been found to occur. In his invaluable book, *Frühentwicklung, u.s.w.*, published in 1927, Grosser states (p. 207) that: "...junge Stadien mit ausgesprochen kapsulärer Lagerung des Keimes, die vorkommen müssen, wenn es eine primär falsch orientierte Implantation polar differenzierter Eier gibt, sind bisher nicht bekannt".

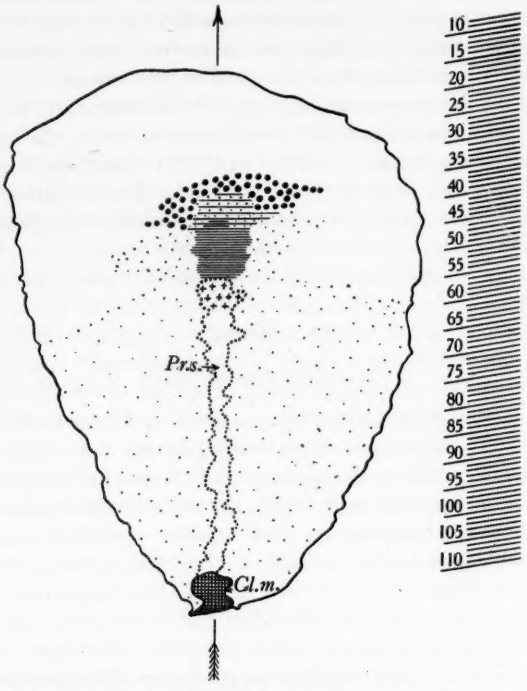
We refer below (p. 407) to the significance of this condition.

THE EMBRYO

(*a*) *Amnio-embryonal vesicle*

The embryo consists of amnio-embryonal and yolk-sac vesicles enveloped by the embryonal mesoderm, and is attached by the short but massive connecting stalk to the upper polar region of the chorion immediately below the capsularis. The amnio-embryonal vesicle is distinctly the smaller of the two. The embryonal shield forming its floor exhibits a definite Hensen's knot (Plate I, fig. 1) situated a little in front of its centre, and extending forwards from the knot, to terminate in the prochordal plate thickening, is the short head-process (text-figs. 1–3). We described the head-process and prochordal plate of this embryo in our paper of 1931 as follows: "So far as we can determine, the head-process is only very little longer than in [Florian's embryo] Bi 24, but it is wider and thicker [Plate I, figs. 2–4]. It is accompanied, as in the latter, by lateral sheets of primitive streak mesoderm, which are much thicker than in Bi 24. Owing to the state of preservation, the limits between the lateral mesoderm and the median head-process are somewhat indistinct in the caudal region. Cranially (text-fig. 5) [our own text-fig. 1], the mesodermal sheets become thinner, and the head-process, which is still thick and compact, is distinctly delimited from them. Still more cranially, at the level of the interrupted line in text-fig. 5 [our text-fig. 1], the head-process broadens out and the lateral sheets of mesoderm practically disappear. We regard the just mentioned line as marking the cranial limit reached by the primitive streak mesoderm accompanying the head-process. Cranially to that line the head-process narrows forward and is surrounded anteriorly and laterally by thickened endoderm, which we interpret as prochordal plate. If this explanation is

right, the prochordal plate [Plate II, fig. 5] appears to be much broader than that of Bi 24, but is of about the same length in the median plane and is in a little more advanced condition" (1931, pp. 467 and 468). We have nothing new to add to this description of the head-process and the prochordal plate. Behind Hensen's knot lies the well-marked primitive streak, here distinctly longer than in the next younger stage so far described, viz. embryo Bi 24



Text-fig. 1. Graphic reconstruction of the dorsal view of the embryonal shield. × 100. The outline of the embryonal shield marked by a thick line. Outline of the primitive streak (*Pr.s.*) and Hensen's knot marked by a dotted line; Hensen's knot marked by crosses. Cloacal membrane (*Cl.m.*) cross-hatched. Head-process marked by horizontal lines closely arranged in its compact, thicker caudal part (chorda process), more widely spaced with dots between, in its wider and more loosely constituted cranial part. Prochordal plate marked by large dots. Secondary mesoderm below the embryonal shield marked by fine dots. On the right of the figure, levels of sections 8–110 are indicated. Median plane marked by an arrow.

(Florian). At its caudal end, a distinct cloacal membrane is developed (text-figs. 1–3, *Cl.m.*), its two constituent layers having become artificially separated in its caudal half.

In text-fig. 1 we have indicated by fine dots the area which we regard as occupied by mesoderm of primitive streak origin. Laterally to the primitive streak, the mesoderm would seem to reach the lateral margins of the embryonal

area, whilst in front of Hensen's knot it extends forwards alongside the head-process as two lateral wing-like extensions. Even in well-preserved embryos, the limits between the primitive streak mesoderm and the primary mesoderm are difficult to determine, and in this specimen, the limits we have indicated in text-fig. 1 must be regarded as approximate only.

In front of the area in which we consider primitive streak mesoderm is present below the shield-ectoderm, we find the primary mesoderm occupying a zone situated around the cranio-lateral margin of the embryonal shield, whilst an area situated in front of, and laterally to, the prochordal plate is practically devoid of mesoderm.

The ectoderm of the embryonal shield passes at its lateral and cranial margins rather abruptly into the very flattened ectoderm of the amnion, and, at its caudal margin, into the stalk-ectoderm. The latter covers the cranio-proximal part of the umbilical stalk (see Florian, 1930, p. 457) and is composed of a layer of rather high cells with an irregular inner contour. Some of the cells seem to be in process of being shed into the amniotic cavity. In the caudal part of the latter is a quantity of cellular detritus (Plate II, fig. 8), very probably derived from these desquamated cells. A similar detritus has been found in the amniotic cavity in other embryos of about this stage of development. In connection with this phenomenon, we may direct attention to the occurrence in sections 77–83 of a small rounded piece of stalk-mesoderm, covered with flattened stalk-ectoderm which projects into the amniotic cavity and is evidently destined to be liberated into the same. Florian (1930) has described a comparable separation of stalk-mesoderm in his embryo Bi XI (with ten paired somites). Here a much larger portion of stalk-mesoderm was found lying free in the amniotic cavity. According to Florian, this separation is effected by the activity of the stalk-ectoderm which penetrates into the stalk-mesoderm, and its object is to enable the amniotic cavity to expand at the expense of the tissue of the connecting stalk so as to provide room for the development of the tail-end of the embryo.

As can be seen in text-fig. 2, the amniotic mesoderm near the attachment of the amnion to the connecting stalk (between sections 66–53) is distinctly thicker than in the more cranial part of the amnion. In the sections it can be seen that between the mesodermal and ectodermal layers of the amnion there is present a thick layer composed of a network of fibrillae. We have here to do with a mesostroma in which the fibrillae, for the most part, run radially to the surface of the amnion, i.e. pass from the mesoderm to the ectoderm. Fahrenholz (1927) described this "thickening" under the name "Aufhängeapparat" ("suspensory apparatus"). It is developed in all specimens belonging to this developmental stage. In the sections, traces of the "suspensory apparatus" can be followed cranially to about section 37. Still more cranially, the mesoderm seems to be composed of a flattened layer of cells situated close to the flattened amniotic ectoderm.

(*b*) *Yolk-sac*

The structure of the ventral wall of the yolk-sac calls for brief mention. Whilst the endoderm of its cranial and lateral walls is formed of flattened cells, that of its ventral wall (beginning at about section 38 and caudally thereto) is distinctly higher. In this same region the mesoderm also becomes markedly thickened; it is composed of loose mesenchyme in which vesicular spaces of varying size are present, and it is produced out into irregular processes so that its surface-contour is extremely uneven (text-fig. 2 and Plate II, fig. 8, *m.*).

This thickened region would seem to correspond with the site of origin of the yolk-sac process of other early embryos.

The thickening of the endoderm becomes specially marked over a medio-ventral area extending from about section 69 back to about section 104. Here the endoderm is irregularly folded and provided with small diverticula (Plate II, fig. 8, *d.e.*); its cells are columnar and contain numerous vacuoles, sometimes quite large, and also coarse spherules, often with smaller deeply staining granules inside them. These spherules appear to be shed into the yolk-sac cavity and to give rise to a coarse detritus, readily distinguishable from the very fine granules derived from the coagulated yolk-sac fluid.

Between sections 94–101 in this same region of the yolk-sac, a curious villous-like process composed of vacuolated cells projects freely from the endoderm into the yolk-sac cavity. Its stalk of attachment is so thin that it might easily become free in the latter.

Behind section 104, the columnar endoderm of the ventral wall gives place to cubical, and caudally to section 119, the latter passes over into the flattened epithelium of the caudal wall.

It remains to be mentioned that vessel-primordia are in process of differentiating in the mesoderm of especially the ventral and lateral parts of the yolk-sac wall.

Allantoic canal

Directly behind the cloacal membrane, a small area of the endoderm of the dorsal wall of the yolk-sac is definitely thickened and exhibits near its centre a minute funnel-shaped opening. This leads into a tubular diverticulum, the allantoic canal, which runs vertically upwards in the mesenchyme of the connecting stalk, immediately behind the caudal extremity of the amniotic

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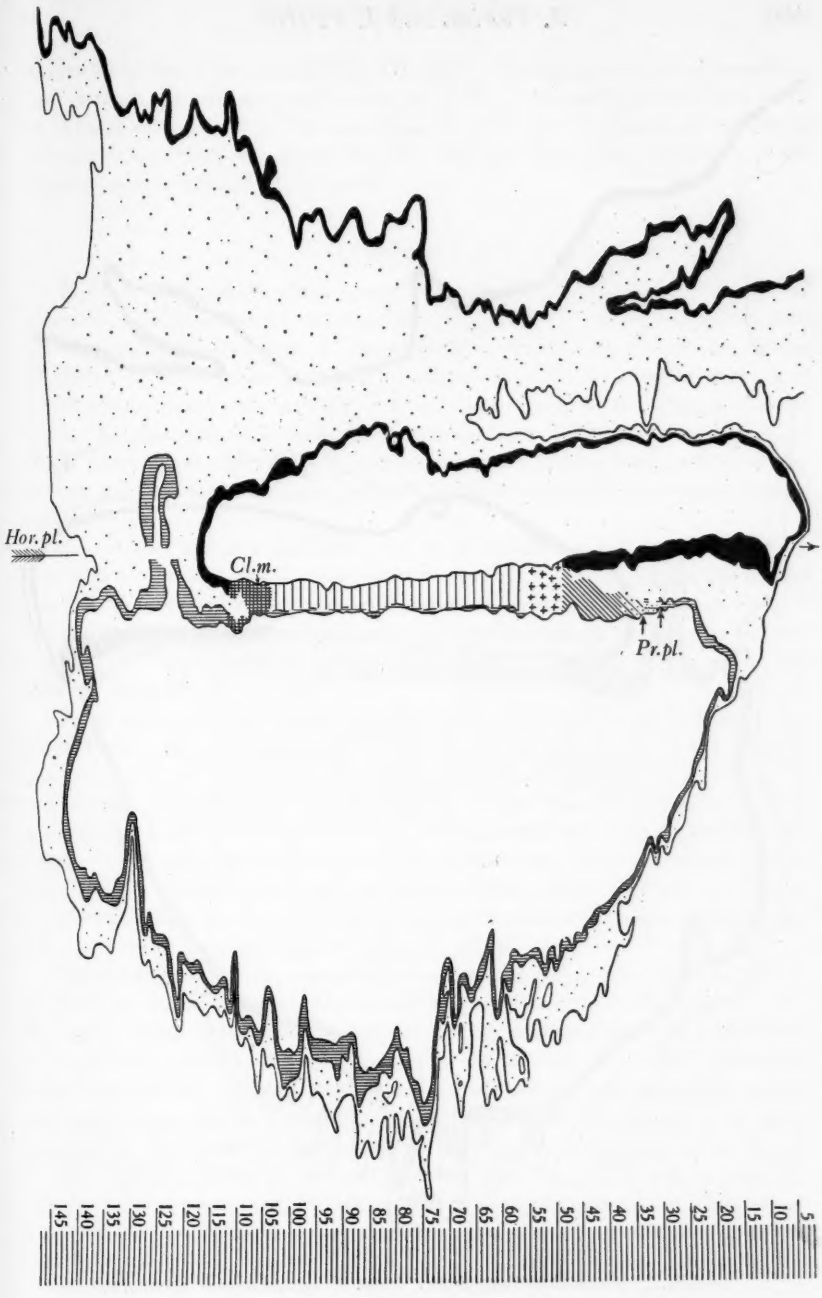
Legend to Text-fig. 2.

Text-fig. 2. Graphic reconstruction of the median section. × 100. Ectoderm black. Endoderm indicated by horizontal lines. Primary mesoderm dotted. Primitive streak marked by vertical lines. Cloacal membrane (*Cl.m.*) cross-hatched. Hensen's knot marked by crosses. Head-process marked by oblique lines closely arranged in its compact, caudal part, more widely spaced and with dots, in its wider and looser cranial part. Prochordal plate (*Pr.pl.*) marked by horizontal lines and dots. Horizontal plane (the plane of projection of text-fig. 1) marked by an arrow (*Hor.pl.*). Levels of sections 2–147 indicated on the scale below the text-figure.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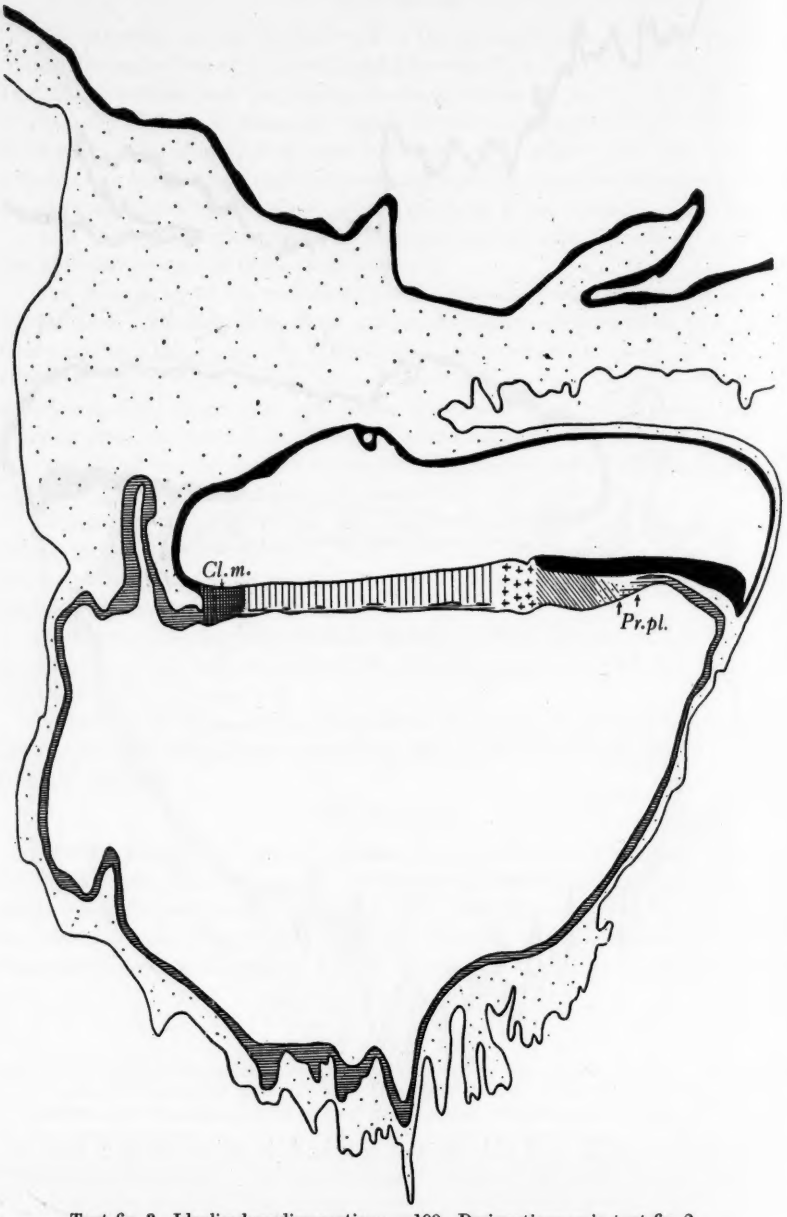
Text-fig. 2.



Text-fig. 3. Idealised median section. ×100. Designations as in text-fig. 2.

cavity (text-figs. 2 and 3 and Plate III, fig. 9). The separation of the canal into two parts in the sections is obviously an artifact. Its wall is formed of a layer of cubical endoderm which is somewhat thinner over the lower two-thirds of its cranial wall than elsewhere, with the result that the upper extremity of the canal appears bulbously thickened.

Connecting stalk

The connecting stalk of our specimen is comparatively short but is of considerable cranio-caudal extent, since its attachment to the amnion begins near the mid-region of the latter. It contains distinct vessel-primordia. In section 97 (Plate II, fig. 7), the primordia of the two umbilical arteries (*u.a.*1 and *u.a.*2) are distinctly visible. They can be traced nearly to the chorionic membrane. In this section, a narrow deep involution of the mesothelium (*v.p.*) of the connecting stalk suggests the participation of that layer in the formation of the umbilical vessels, as is believed to be the case in other early human embryos.

As we have already indicated, the most interesting feature exhibited by this embryo is provided by the attachment of the connecting stalk to the chorion. Whereas in other described early embryos this attachment lies adjacent either to the decidua basalis or to the marginalis, in the present embryo it occurs below the decidua capsularis in a position diametrically opposite the basalis (Plate III, fig. 11, *c.s.*).

As in the normally attached embryo, the villi below the capsularis are much less developed than those in relation to the marginalis and basalis. Whilst the latter villi are elongated and exhibit distinct branching and are disposed more or less perpendicularly to the chorionic surface, those below the capsularis are smaller, less numerous, are much less branched and tend to be disposed tangentially to the chorion owing to the narrowness of the intervillous blood-space. From the area of the chorion to which the connecting stalk is attached a few small villi originate, but immediately to the left of the area of attachment is a small circumscribed region wholly devoid of villi.

The attachment of the connecting stalk to the upper or capsularis pole of the chorion where obviously the definitive placenta cannot develop, provides the explanation of the polar variety of the so-called insertio velamentosa of the umbilical cord, i.e. the condition in which the umbilical cord is attached to the chorion laeve opposite the placenta, and the umbilical vessels traversing that membrane enter and leave the organ all round its circumference. This same explanation has already been advanced by other workers, notably R. Meyer (1923), Schmidt (1925, p. 666), O. Grosser (1927, p. 396), and is now, we believe, generally accepted, though, as we have already pointed out, the present specimen is the only early embryo in which the capsular attachment has been demonstrated.

Whilst, then, the velamentosous condition may be regarded as satis-

factorily explained, how are we to account for the reversed implantation in the present specimen? We have no satisfactory explanation, beyond that of a chance happening. The deep-seated position of the embryonal primordium in the chorionic vesicle, adjacent to the decidua basalis, is generally ascribed to the coincidence of the upper pole with the implantation pole, i.e. to the fact that they are one and the same. In our specimen it would seem that this coincidence for some reason failed and the lower pole functioned as the implantation pole. We are assuming that implantation is effected during the early blastocyst stage when the attachment of the inner cell-mass (embryoblast) clearly differentiates the poles and that normally implantation is a function of the trophoblast of the upper pole. On the other hand, if implantation takes place during the morula stage, and if the poles of the morula are already predetermined, another possibility suggests itself to the effect that when the blastocyst cavity appeared, the inner cell mass adhered to the trophoblast of the lower pole instead of to that of the upper as is normal. In this case we should be dealing in our specimen with an apparent, not a real, reversal of the polarity of the chorionic vesicle.

Like Grosser (1927, p. 212), we are quite unable to accept the ideas put forward by v. Möllendorff (1921, 1925, 1926) to account for the position of the embryo at the deep pole of the chorionic vesicle. He holds that the embryoblast is originally intercalated in the trophoblast, and during implantation is the last part to enter the decidua. The embryonal primordium is thus originally situated below the capsularis, and he supposes it reaches its normal position in relation to the basalis either through the rotation of the chorionic vesicle as a whole or by the active migration of the primordium by way of the chorionic mesoderm to its final site. In our opinion, if such a change in the position of the embryonal primordium occurs at all, which we very much doubt, it could only be effected by the unequal growth of the chorion and not in either of the ways envisaged by v. Möllendorff. In any case we hold that the original attachment of the embryoblast to the trophoblast also marks the site of attachment of the later developed connecting stalk to the chorion, and in proof thereof we would point to the fact that the amniotic duct which we regard as owing its origin to that primary attachment, is always situated in the connecting stalk mesoderm.

Decidua

The decidua shows the typical characters of the premenstrual phase. The vesicle occupies nearly the whole thickness of the compacta, only a thin layer of the same underlying it. The epithelium of the glands exhibits the characteristic folding and the gland-lumina contain secretory coagulum and sometimes also extravasated blood. The decidual reaction is indicated in the decidua basalis and in the marginalis on the right side next the groove as well as in the decidua parietalis on the same side, but is little evident in the decidua capsularis and in the marginalis on the left side. This latter region presents an

oedematous appearance, and both it and the capsularis contain blood-extravasations. Large numbers of leucocytes are present in the extravasated blood in the glands as well as in the decidual tissue, especially in the marginalis and the adjacent capsularis on the left side of the vesicle.

The capsularis is somewhat damaged and in the sections is partially separated into a poorly preserved outer zone containing much fibrinoid and a deep zone in rather better condition. Adjacent to the attachment of the connecting stalk, a thick flake-like portion of the outer zone, composed largely of fibrinoid, with only a few cells imbedded in it, is separated off in the sections. In places in the deep zone, traces of what Florian (1928) has termed the "Proliferationsplasmodium" are recognisable. An epithelial layer is not distinguishable over the capsularis.

Decidual vessels. A number of small vessels of the nature of distended capillaries lead from the basalis to open into the intervillous blood space at the deep pole of the vesicle. In the interglandular tissue of the basalis itself, numbers of small arterioles and venules are present, but taken as a whole, the portion of the basalis available to us is entirely devoid of large vessels and cannot be described as richly vascularised. On the other hand, it is noteworthy that the only conspicuously large vessels in the immediate proximity of the vesicle are situated in the capsularis and in the marginalis on its left side. We regard these vessels as veins. They are enlarged and sinus-like, and their lumina are largely occupied by blood-corpuscles (Plate III, fig. 11, *cv.*, *cv.*[1]). The largest of these veins is situated in the capsularis adjacent to the attachment of the connecting stalk (Plate III, fig. 11, *cv.*). It can be traced from behind the embryonal primordium forwards to its cranial extremity but is much reduced in diameter in the more cranial part of its extent. In the capsularis, to the left of this main vein, there are present smaller veins (Plate III, fig. 11, *cv.*[1]) which open into it as well as into the intervillous blood space on the upper left side of the vesicle, whilst they are also connected with a well-marked vein which passes almost vertically downwards in the marginalis (Plate III, fig. 11, *mv.*).

Chorion and villi

The chorion and villi exhibit the normal structure, the chorionic mesoderm being well developed. Round the periphery of the implantation cavity and between the extremities of the villi, there occur numerous irregular masses and strands of syncytio-trophoblast and also irregular disconnected masses of cytotrophoblast representing the remains of the basal trophoblast of earlier stages. The syncytio-trophoblast is most abundant on the surface of the basalis underlying the more cranial part of the vesicle. Plate III, fig. 10, from section 23, shows a canalised mass of it penetrating into a distended capillary in the basalis.

SUMMARY

The specimen described was obtained from a case of total uterine extirpation and comprises the chorionic vesicle with the surrounding decidua and the contained embryo. The latter in its stage of development lies between Florian's embryo Bi 24 and Grosser's embryo Wa 17. It is unique in that its connecting stalk is attached to the chorion not at its deep (basalis) pole as is normal but at its superficial pole underlying the capsularis. It thus provides the explanation of the polar variety of insertio velamentosa of the umbilical cord.

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EXPLANATION OF PLATES I–III

PLATE I

Fig. 1. Section 49, passing through the cranial extremity of Hensen's knot, which is situated between arrows 2 and 3. The lateral margins of the primitive streak mesoderm are indicated by arrows 1 and 4. ×391.

Fig. 2. Section 43, passing through the caudal, more compact part of the head-process (chorda-process), situated between arrows 2 and 3. The lateral margin of primitive streak mesoderm indicated by arrow 1; the margin on the other side is not included in the figure. ×391.

Fig. 3. Section 40, passing through the more cranial part of the chorda-process. Designations as in fig. 2. ×391.

Fig. 4. Section 37, passing through the wider, less compact cranial part of the head-process (between arrows 2 and 3). The lateral margins of primitive streak mesoderm indicated by arrows 1 and 4. *ek.*, ectoderm of the embryonal shield, artificially detached from the underlying tissue. ×391.

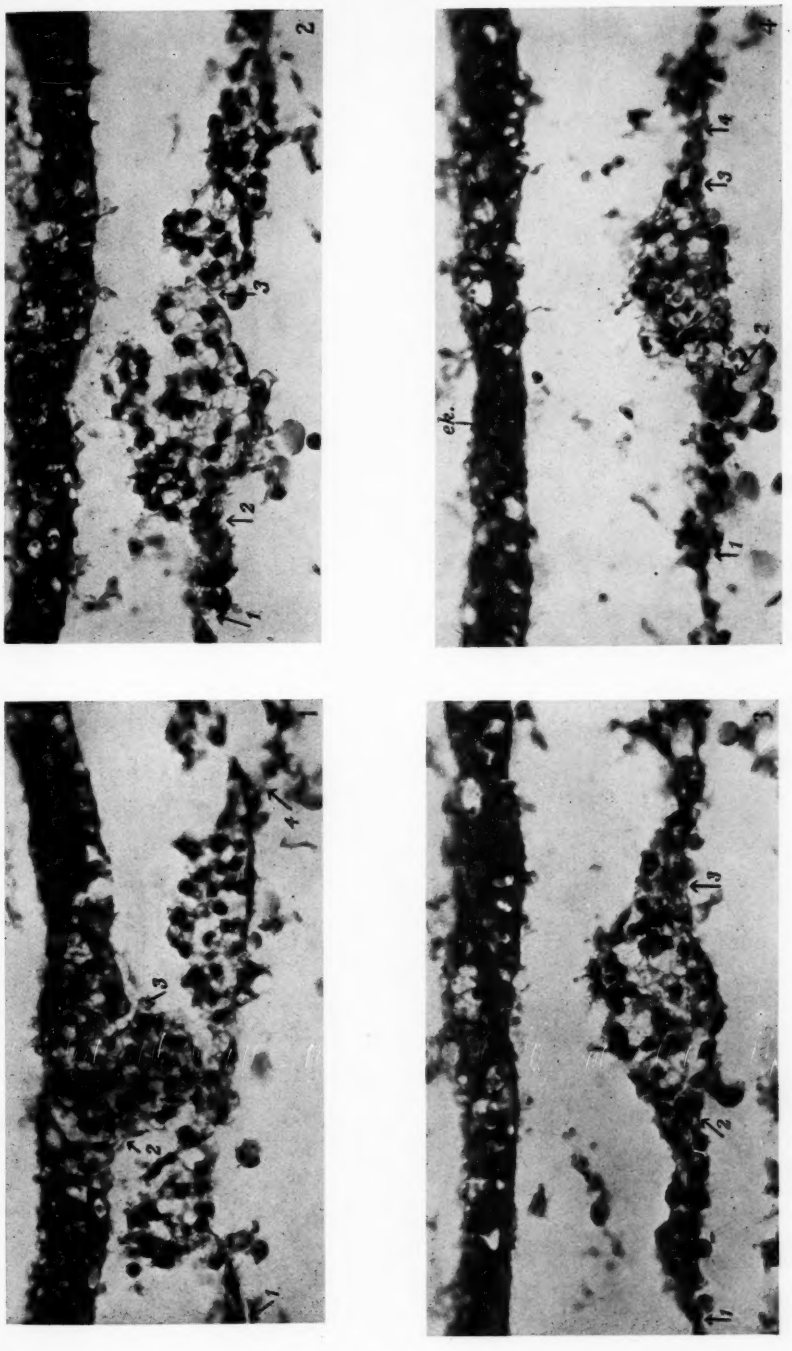
PLATE II

Fig. 5. Section 32, passing through the prochordal plate and the cranial extremity of the thin part of the head-process (between arrows 1 and 2). ×391.

Fig. 6. Section 79, passing through the sequestered mesoderm of the connecting stalk (above "*s.c.s.*"). *a.c.* amniotic cavity. *s.e.* stalk-ectoderm. *s.m.* stalk-mesoderm. Dorsal side above. ×391.

Fig. 7. Section 97, passing through the connecting stalk and the primitive streak. In the connecting stalk, the primordia of the umbilical arteries (*u.a.*1 and *u.a.*2) can be seen. The mesothelium of the connecting stalk shows a deep invagination at *v.p.* (vessel-primordium). *a.c.* amniotic cavity. *p.s.* primitive streak. ×115.

Fig. 8. Section 75, passing through the ventral wall of the yolk-sac (see text, p. 404). *y.s.c.* = yolk-sac cavity. *en.* endoderm. *d.e.* diverticulum of the endoderm directed towards the mesoderm. *m.* mesoderm. ×186.



FLORIAN AND HILL—AN EARLY HUMAN EMBRYO

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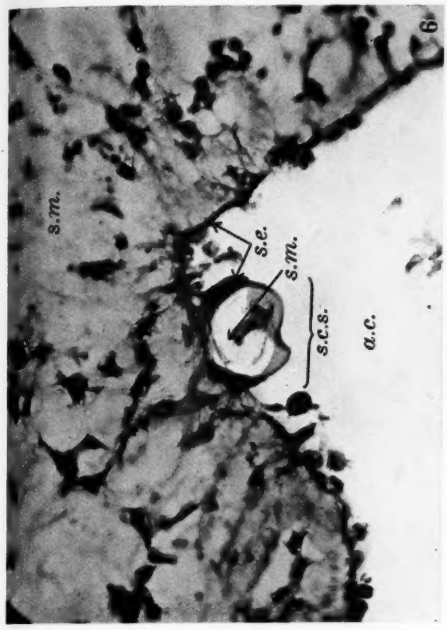

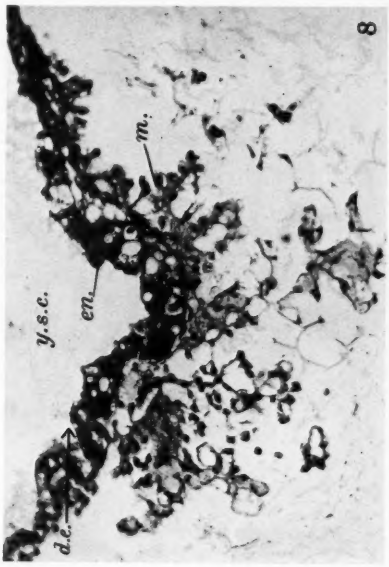

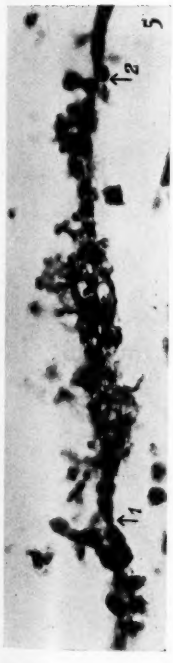

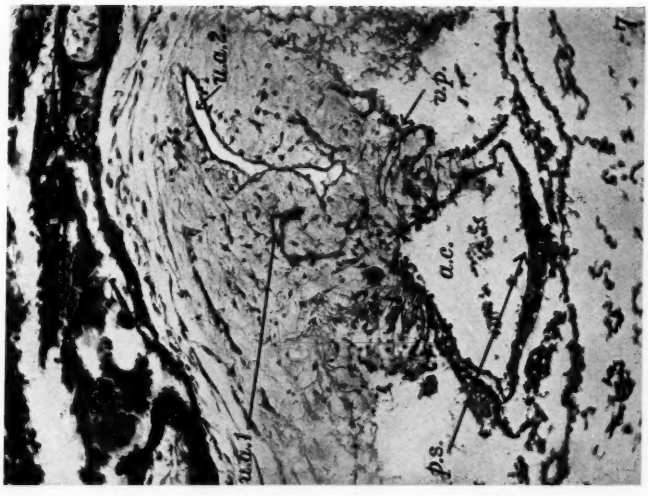

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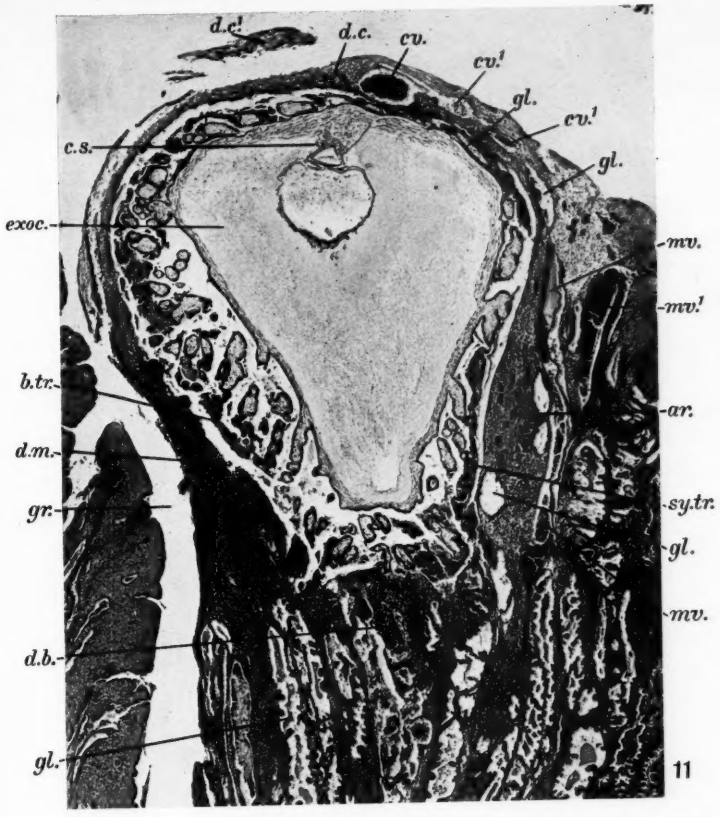
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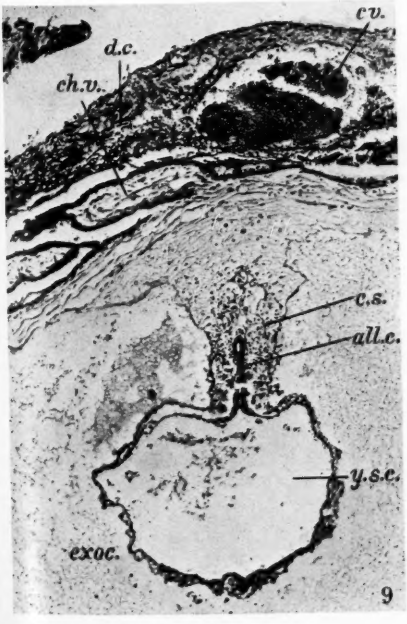
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PLATE III

Fig. 9. Section 122, passing through the connecting stalk (*c.s.*) and the allantoic canal (*all.c.*). *ch.v.* chorionic villus. *cv.* vein in decidua capsularis (*d.c.*). *exoc.* exocoelom. *y.s.c.* yolk-sac cavity. ×48.

Fig. 10. Section 23. A large mass of syncytio-trophoblast is invading a distended capillary (*c.*). *i.* intervillous space. *gl.* uterine gland. ×104.

Fig. 11. General sectional view of the chorionic vesicle and the surrounding decidua. The section (99) passes through the embryonal primordium at the level of the hinder end of the primitive streak and shows the amnio-embryonal vesicle, here much reduced in size, the very much larger yolk-sac vesicle and especially the connecting stalk attached to the chorion below the central region of the decidua capsularis. *ar.* arteriole in d. marginalis. *b.tr.* basal trophoblast. *c.s.* connecting stalk. *cv.*, *cv.*^{1} veins in d. capsularis (*d.c.*). *d.c.*^{1} portion of capsularis artificially separated. *d.b.* decidua basalis. *d.m.* d. marginalis. *exoc.* exocoelom. *gl.* uterine gland. *gr.* groove in decidua. *mv.*, *mv.*^{1} veins in d. marginalis. *sy.tr.* syncytio-trophoblast. ×16.

THE FORMATION OF THE VENOUS VALVES, THE FORAMEN SECUNDUM AND THE SEPTUM SECUNDUM IN THE HUMAN HEART

By P. N. B. ODGERS

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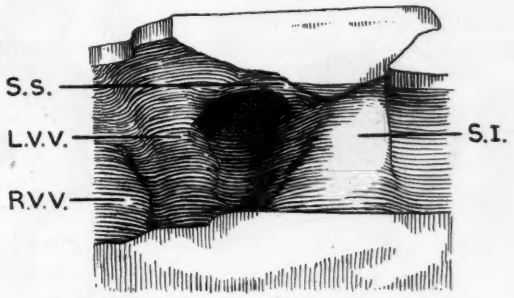
So many of the details in the development of the heart have been worked out in the chick or in such Mammals as the rabbit or the pig, that it seemed worth while to attempt the re-investigation of some of them in human embryos. For this purpose I made use of the following material in this department: human embryos of 5, 6·5, 7·1, 11·2, 14, 17·5, 23, 28·5, 46 and 61 mm. in crown-rump length. Reconstruction models of the venous end of the heart were made from the 5, 7·1, 11·2, 17·5, 28·5 and 46 mm. specimens. I also had the opportunity kindly afforded me by Prof. J. Ernest Frazer of studying from his extensive series the hearts in a 4·5- and a 4·9-mm. embryo, in two 5-mm. and two 8-mm. embryos and in a 9-mm. embryo.

I. THE FORMATION OF THE VENOUS VALVES

Waterston (1918) described both the venous valves as formed by the invagination of the right horn of the sinus venosus into the right auricle. While this is certainly so in the case of the right valve, the left one has, I consider, an entirely different origin. The right valve is originally the coapted walls of sinus and auricle and increases in size with the increasing intussusception of the former into the latter chamber. A well-defined groove on the outer surface of the models of the 5- and 7·1-mm. stages marks the sinu-auricular junction and the site of the right valve, and this is seen in Plate I, fig. 5.

The left valve, on the other hand, is derived as a delamination of the septum primum. It appears in my 5 mm. model (text-fig. 1)—I could find no trace of its formation in Frazer's 4·5- or 4·9-mm. embryos—as a ridge, most pronounced above, anterior to the sinu-auricular orifice and the right venous valve. At this stage it is the more prominent of the two valves. Above, its anterior border is connected with the septum primum by an elevation arching forwards, which bounds the commencing intersepto-valvular space and is the beginning of the septum spurium or tensor valvulae. Below it merges into the expanded base of the septum. There is no external sulcus corresponding to the site of the left valve like that described above for the right one. As I interpret them its formation is well shown in the microphotographs reproduced in Plate I. The septum primum is formed in a line of stasis, due apparently to the attachment of the mesocardium dorsally and the formation ventrally of the upper (or dorsal) auriculo-ventricular endocardial cushion. On either side of this stasis

line the auricles are free to expand. Into the subendocardial space here the myocardium proliferates, commencing first, as is seen in Frazer's 4·9-mm. specimen, at the attachment of the mesocardium and spreading up on to the roof from here (Plate I, fig. 1). The succeeding three figures in Plate I, which are photographs of alternate sections next below fig. 1, show that a lacuna appears so that the myocardial proliferation is divided into right and left portions, which gradually separate entirely from each other. The left limb forms the septum primum, the right limb the left valve, while the connection between the two is the anlage of the septum spurium. This latter, as my model shows well, is at this stage continuous with the left valve alone and has no connection with the right one. These observations were confirmed in one of Frazer's 5-mm. hearts, which presented precisely the same appearances. In another 5-mm. specimen of his the condition of the valve was more advanced and resembled that seen in my 6·5-mm. embryo. In the 6·5- and 7·1-mm. stages the increasing



Text-fig. 1. Drawing of a model of the auricles in a 5-mm. embryo. The centre portion of the posterior wall is represented, viewed from the front. *S.I.* septum primum; *S.s.* septum spurium; *R.V.V.* right venous valve; *L.V.V.* left venous valve.

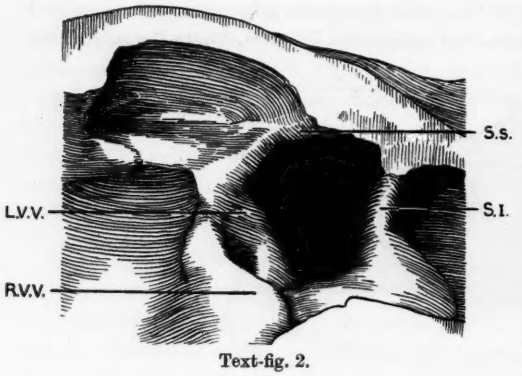
invagination of the right sinus horn, which has made the right valve, projecting now well in front of the left, the more prominent of the two, has also reached and taken up the left venous valve so that the latter now forms the left lip of the sinu-auricular opening (text-fig. 2). The extraordinary increase in the height and depth of the intersepto-valvular space must also be a subsidiary factor in producing this change. The upper ends of both valves have now joined each other in a common superior fornix. To this the left valve has brought with it the septum spurium, which still runs anteriorly into the septum primum and thus still betrays the septal origin of the valve. Below, the left valve still ends in the expanded base of the same septum.

Chang (1931) has given an account of the formation of the left venous valve in the chick's heart, which in some ways seems to be comparable to mine. He described it as being formed in two stages. First at 62 hours of incubation the endocardial proliferation along the ventral end of the dorsal mesocardium, which is going to form the septum primum, makes the temporary left boundary

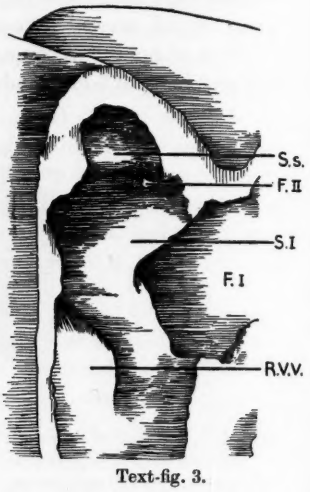
of the sinu-atrial opening. The permanent left valve arises later at 96 hours of incubation from the dorsal atrial wall and is continuous caudally with the earlier formation.

II. THE FORMATION OF THE FORAMEN SECUNDUM

The first appearance of this was found in my 7·1-mm. specimen. There was no sign of it in any of the earlier embryos I examined. Here, close to the junction of the anterior end of the septum with the roof, a small hole is seen which extends over two sections only (text-fig. 3). It seems to be formed in this way. In my description of the formation of the left venous valve I have shown



Text-fig. 2.



Text-fig. 3.

Text-fig. 2. Drawing of a model of the auricles in a 7·1-mm. embryo. The centre portion of the posterior wall is represented, viewed from the front. *S.I.* septum primum; *S.s.* septum spurium; *R.V.V.* right venous valve; *L.V.V.* left venous valve.

Text-fig. 3. Drawing of a model of the auricles in a 7·1-mm. embryo, viewed from the right side, to show the commencement of the foramen secundum. *S.I.* septum primum; *S.s.* septum spurium; *F.I.* foramen primum; *F.II.* foramen secundum; *R.V.V.* right venous valve.

that the myocardium proliferates into the septum primum from the dorsal wall of the auricle. At the 6·5-mm. stage, as is seen in the microphotograph of the septum (Plate II, fig. 1), the dorsal outgrowth is met by a smaller pyramidal proliferation from the ventral wall. The section which is figured is four sections above the foramen primum and, as this is approached, the ventral outgrowth becomes less and less obvious until it finally fails to meet the dorsal one and the foramen occurs. Three sections above the level of that photographed the two projections, dorsal and ventral, have so perfectly blended that the septum appears to be composed of a continuous myocardial layer. The appearance presented by similar sections in my 7·1-mm. embryo is very much the same.

In the series of microphotographs (Plate II, figs. 2–10) the dorsal and ventral myocardial outgrowths are seen at first four sections above the foramen secundum. At this level (Plate II, figs. 2–3) they meet but are not in accurate contact, the ventral proliferation being slightly to the left of the dorsal one. The contact between the two becomes less and less until a foramen, the foramen secundum, occurs. Below this the two outgrowths meet again in the same line for three sections, when the ventral outgrowth decreases and the foramen primum appears. The cause of either foramen, primum or secundum, seems to be the same, namely the failure of the dorsal and ventral proliferations to make contact. The only difference between the two levels is that, while in the case of the foramen secundum the dorsal proliferation seems to be at fault, in the case of the foramen primum, as was previously noticed in the earlier 6·5-mm. specimen, the ventral outgrowth is the one that fails. I would suggest then that the foramen secundum is due to a local failure of growth to complete the septum rather than that it is caused by the localised destruction of a septum previously perfect or, expressed differently, the foramen secundum is a portion of the foramen primum which has not been obliterated. I can see no ragged edges to the foramen as Waterston described in his 6-mm. heart. Both projections are clearly defined with intact endocardium.

As will be realised, these observations of mine are entirely heterodox. While Born (1888) wrote of the foramen secundum as "appearing", Tandler (1912) and all other observers since have described it as a gradual thinning and final break through of the septum primum. The only paper I have come across in which any doubt is expressed about this question is one by Retzer (1908), who in his description of the formation of the foramen secundum in the pig's heart wrote: "I am at present unable to say whether the perforation one sees is due to a rupture of the thin lamella, which at first consists of but two rows of cells, or is actually an opening formed during the growth of the heart." I am not sure that I cannot find some indirect support in the observations of Röse (1890) on the comparative embryology of the heart. In Birds, Monotremes and Marsupials he described the secondary break through of the septum primum as being closed quite quickly by the growth of the endocardium. In the heart of the calf, sheep and horse there are multiple openings in the septum, which together represent the foramen secundum, the smaller ones of these being obliterated subsequently, according to his account, by endocardial proliferation. This description suggests at all events that there is some active proliferation going on, and I would suggest that multiple openings could *a priori* be expected to result rather from a local failure of growth than from multiple perforations of a once perfect septum. I cannot find anywhere any figures showing the commencement of the foramen secundum. In an 8-mm. embryo of Frazer's which I examined it is already a large hole in the septum, and all the text-book illustrations figure it at this or at a somewhat later stage. I think this may be the reason for both Born and Tandler describing its commencement as occurring more posteriorly than it does. Born (1889) in the rabbit described it as

appearing where the posterior auricular wall curves into the roof, while Tandler in Keibel and Mall wrote that it is formed "either directly at the line of origin of the septum on the posterior upper wall of the atrium or immediately below it".

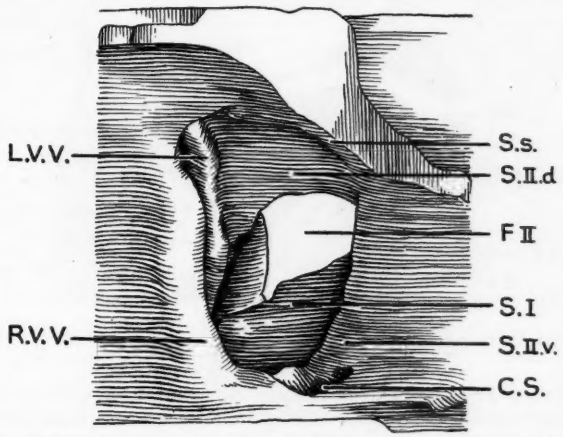
It is interesting to speculate as to the reason why the foramen primum should normally close, while the foramen secundum should appear and so quickly become a large opening. Possibly the direction of the blood stream may be the causal factor. At 5 mm. the widest part of the sinu-auricular opening is in the floor of the right auricle; the rest of it is a mere chink. At this stage the blood stream is directed chiefly to the roof and may be responsible for the delamination of the septum, the appearance of the left venous valve and of the intersepto-valvular space. At 7·1 mm. the right venous valve has advanced so far into the right auricle and has come up so much on its floor that its tip reaches to the same level as the anterior border of the septum primum. The sinu-auricular opening is now wider on the posterior wall than on the floor, and the blood stream is directed by the right valve to the left against the septum rather than against the roof. The foramen primum is thus in front of the main blood flow and can close perhaps, as Waterston suggests, chiefly by the increase in size of the endocardial auriculo-ventricular cushions, and their extension dorsally, while the foramen secundum bears increasingly the brunt of the blood stream and is increasingly irrupted.

III. THE FORMATION OF THE SEPTUM SECUNDUM

At the 7·1-mm. stage the groove in the roof which marks the separation of the two auricles corresponds accurately to the line of the septum primum. In the 11·2-mm. model this inter-auricular cleft is obviously to the right of the septum primum and is in the same plane as the septum spurium and the left venous valve, the septum primum being laid back almost against the dorsal wall of the left auricle with the pulmonary vein opening into the narrow cleft between the two. Frazer (1931) suggests that this change is due to the left auricle increasing the area of its roof towards the right. I would rather put it down to the counter-clockwise rotation of the auricles, which seems to be due primarily to the increasing projection of the right horn of the sinus venosus and its valves into the right auricle, the tip of the right venous valve actually projecting into the right auriculo-ventricular orifice at this period. The stage is thus set, so to say, for the formation of another septum. At 17·5 mm. the first definite indication of the septum secundum is seen as a projection into the intersepto-valvular space from the dorsal wall of the right auricle close to the roof to the left of the septum spurium (Plate III, fig. 1). Corresponding to this projection there is a very definite inflection of the auricular wall at its junction with the right sinus horn. Traced caudalwards, the incipient septum soon blends with the left side of the left venous valve. Further in this same heart another projection is to be seen from the ventral wall. This arises from the dorsal border of the septum intermedium—a convenient term I think to retain

for the fused auriculo-ventricular cushions—just to the right of the septum primum in the lower part of the intersepto-valvular space (Plate III, fig. 2). It can be traced through ten sections and blends, as it flattens out, with the extremity of the left venous valve. Something comparable to this is to be observed in my 11·2-mm. embryo. In this latter there is a knoblike projection from the right side of the lower part of the septum primum close to its union with the septum intermedium. This is figured in Plate III, fig. 3, and can be seen in seven sections above and in three sections below that photographed before it flattens out in the auriculo-ventricular cushions.

In my 28·5-mm. embryo the septum secundum is much further developed and forms at this stage with the left venous valve a complete circular dia-



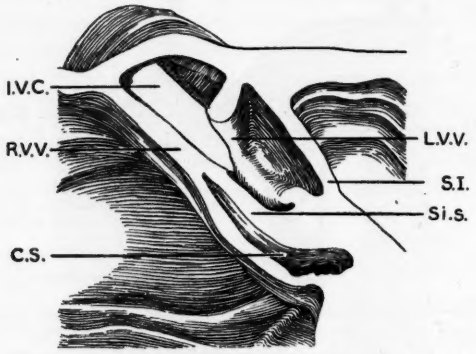
Text-fig. 4. Drawing of a model of the auricles in a 28·5-mm. embryo, viewed from the right side, to show the venous valves and the septal formations. *S.I.* septum primum; *S.s.* septum spurium; *F.II.* foramen secundum; *R.V.V.* right venous valve; *L.V.V.* left venous valve; *C.S.* coronary sinus; *S.II.d.* septum secundum, dorsal segment; *S.II.v.* septum secundum, ventral segment.

phragm (text-fig. 4). As I interpret it, the septum secundum appears to consist of two parts. The dorsal segment springs from the posterior wall at its junction with the roof in exactly the same plane as the interauricular cleft. It arches over the roof of the auricle to the left of the left venous valve, which is quite a distinct projection on its right side. Just where the ventral wall of the auricle joins the roof this dorsal portion meets the upper end of a ridge projecting from the ventral wall. As this ventral moiety of the septum is traced caudalwards it becomes more prominent and ends in a bifurcation, becoming continuous by its larger right limb with the sinus septum and by its smaller left limb with the left venous valve. The latter forms with the lower end of the septum primum a little bay, which projects into the opening of the inferior vena cava and represents the caudal extremity of the intersepto-valvular space

(text-fig. 5). My reasons for suggesting that the septum secundum is composed of two separate outgrowths here are:

(1) While the dorsal segment is most marked above, the ventral segment increases in thickness as it is traced caudally. Where these two meet at the anterior superior angle, the septal projection is minimal.

(2) The two ridges are not accurately in the same plane, the ventral outgrowth being slightly to the right of the dorsal one. Their relations therefore to the left venous valve are different. This valve is on the right of the dorsal moiety, while its termination runs into the left limb of the bifurcating ventral projection. While the septum spurium (tensor valvulae) ends anteriorly just above the upper extremity of the ventral half of the septum secundum, it appears in my model as a distinct ridge arching over the auricular roof to the

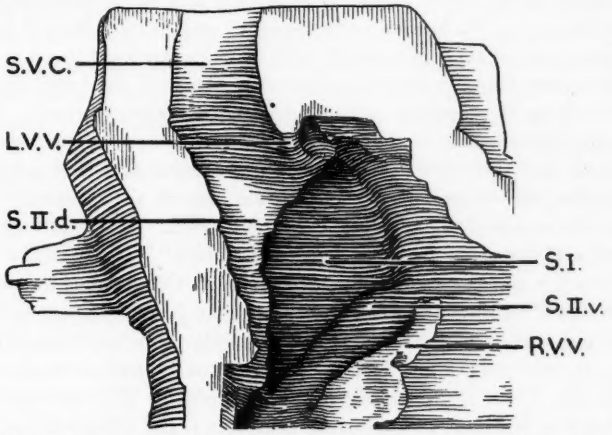


Text-fig. 5. Drawing of the lower portion of the same model as text-fig. 4, of a 28·5-mm. embryo, to show the termination of the left venous valve. This section is immediately below that represented in text-fig. 4 and is viewed from above. *S.I.* septum primum; *Si.s.* Sinus septum; *C.S.* coronary sinus; *R.V.V.* right venous valve; *L.V.V.* left venous valve; *I.V.C.* inferior vena cava.

right of this septum, which seems to be entirely independent of it in its formation. Favaro (1913) found that in the guinea-pig and sheep the septum spurium joins the newly formed septum secundum. While Morrill (1916) noted that this does not occur in the pig's heart, he suggested that in the human embryos he examined its course and relations seemed to be more like those described by Favaro in the guinea-pig and sheep.

In my 46-mm. specimen (text-fig. 6) the development of the septum secundum appears to be less advanced in most respects than in the previous 28·5-mm. embryo. The two projections, dorsal and ventral, which are going to form it have not met and therefore appear the more distinct each from the other. On the other hand, there is no obvious left venous valve except above and below. Above, the notching of the anterior border of the dorsal projection indicates its compound origin, while below, the termination of the valve now appears as a ridge running almost at right angles to the lower end of the septum

secundum towards the caudal and dorsal border of the septum primum. This ridge projects into the dorsal wall of the inferior vena cava just where it is opening into the auricle and must be the remains of the dorsal half of the bay made by the left venous valve in the 28·5-mm. stage (text-fig. 5). The ventral projection is very prominent below, and while, as in the previous specimen, it is continuous on its right side with the sinus septum, the main portion of it runs as a tapering ridge to join the septum primum. This ridge projecting opposite that on the dorsal wall of the inferior vena cava described above must represent the ventral half of the bay made by the left venous valve in the 28·5-mm. embryo; the rest of the bay has gone and the lower end of the intersepto-valvular space has thus been obliterated.



Text-fig. 6. Drawing of a model of the septal structures in a 46-mm. embryo, viewed from the right side. The right venous valve has been removed. *S.I.* septum primum; *R.V.V.* cut end of right venous valve; *L.V.V.* left venous valve; *S.V.C.* superior vena cava; *S.II.d.* septum secundum, dorsal segment; *S.II.v.* septum secundum, ventral segment.

In spite of such views as those expressed by Retzer (1908), who regarded the septum secundum as a passive formation—"in the pig the septum secundum in Born's sense does not exist: search for it was made in vain in the embryonic hearts of man, monkey and rabbit"—or by Waterston (1918), who suggested that the edge of the limbus fossae ovalis was formed by the fused left venous valve and the remains of the septum primum, while the whole of the dorsal and oral portion of the so-called septum secundum was merely the result of the coaptation of the adjacent walls of the two atria, I think it is generally agreed that the septum secundum is due to a local myocardial proliferation. Born (1889), working chiefly at the development of the rabbit's heart, described it as arising from the roof and the upper part of the posterior wall of the auricle as a crescentic ridge, which grew over the roof and on to its anterior wall, and his account has usually been followed in the description of this septum in the

human heart. There is, however, considerable authority for a ventral origin of this septum in Man and other Mammals. Röse (1890) originally described it as beginning "on the anterior and upper atrial wall, as a ridgelike infolding, the septum musculare, which together with the septum intermedium is formed into a closed ring diaphragm, the annulus ovalis" (Morrill's translation). Morrill (1916), in the pig's heart, found the septum commencing as a spur from the septum intermedium at the anterior inferior corner of the auricle and spreading upwards and backwards along the roof to the posterior wall, where it flattens down and may become continuous with two or three muscular trabeculae in the intersepto-valvular space. He denies, therefore, that in this animal any dorsal outgrowth contributes to the formation of the septum secundum. Favaro's description (1913), based on guinea-pig and sheep embryos, was very similar to the latter. In human embryos of 12 and 14 mm. Morrill noted that "in the lower part of the right auricle of both these embryos there was a thick connective tissue ridge or prominence continuous with the fused endocardial cushions, and partly overlaid and invaded by developing muscle. As in the pig this musculature was continuous with that of the septum primum and the sinus valves. The resemblance between this structure and that described for the pig in the corresponding place is so close that I am inclined to think it represents the origin of the septum secundum in Man." Again, Thyng (1914), in describing a 17·8-mm. human embryo, found that "just where the left sinus valve meets the right side of the septum primum there is a ridge or tubercle which probably represents the caudal end of the future septum secundum". This last observation is apparently exactly similar to what I found myself in my 17·5-mm. specimen (Plate III, fig. 2). Here the projection is into the intersepto-valvular space from the septum intermedium. The only difficulty, if indeed this is a real one, in supposing that this is the commencement of the ventral outgrowth so conspicuous in the 28·5-mm. embryo, is that at the 17·5-mm. stage the projection is to the left of the left venous valve, and one must predicate that, as this outgrowth increases in size, it takes up the anterior attachment of the left valve to bulge more prominently to the right of it.

As the result of my own observations I would maintain that in the human heart there are two discrete outgrowths, a dorsal one and a ventral one, which, meeting at the anterior-superior angle of the auricle, together form the septum secundum.

Lastly, I suggest the probability that this septum is formed ultimately, at all events, from sinus musculature. I cannot prove this, because, while in the earlier stages the sinus myocardium is readily distinguishable from that of the auricle—it is more cellular and stains more deeply—this is not so obvious in the more advanced embryos. The dorsal outgrowth corresponds, as I have said, to an inflection of the sinu-auricular junction, while the incorporation of the left venous valve with it must bring sinus tissue to it. Again, the ventral portion is continuous with the sinus septum and the termination of the left venous valve. Retzer described the invasion of the septum intermedium by the muscu-

lature of the sinus venosus, while Morrill concludes that in the pig a part of this musculature at least thickens to form the root of the septum secundum.

CONCLUSIONS

1. While the right venous valve is formed by the coaptation of the wall of the right horn of the sinus venosus with that of the auricle and grows by the increasing invagination of the former into the latter cavity, the left valve has its origin in a delamination of the septum primum.

2. The appearance of the foramen secundum is due to a local failure of growth of the septum primum rather than to a breakdown of the septum already formed.

3. The septum secundum has a double origin. Not only is there a dorsal outgrowth in association with the upper end of the left venous valve, but there is also a ventral proliferation from the septum intermedium commencing to the right of the anterior inferior angle of the septum primum and blending later with the sinus septum and the lower end of the left venous valve.

I gladly acknowledge the help I have received from Mr W. Chesterman, of this Department, in the making of my models and in the preparation of the microphotographs.

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EXPLANATION OF PLATES I–III

Plate I

Figs. 1–4. These microphotographs of sections of the auricles in a 5-mm. embryo (× 60) show in fig. 1 the myocardium spreading into the subendocardial space from the dorsal wall to form the septum primum. Figs. 2–4 are photographs of alternate sections next below this and in them a lacuna appears in the myocardial proliferation, ultimately splitting this into two. The left limb forms the septum primum, the right limb the left venous valve, the connection between the two persisting as the septum spurium.

Fig. 5 is a microphotograph of the same heart 11 sections below the last. This shows the right valve as being formed by the coaptation of the anterior wall of the right horn of the sinus venosus with the posterior wall of the auricle. The left venous valve is seen as a small projection immediately to the left and slightly anterior to the right valve.

PLATE II

Fig. 1. A microphotograph of the septum primum in a 6·5-mm. embryo (× 124). This is four sections above the foramen primum and shows that the larger dorsal myocardial proliferation is meeting a much smaller cone-shaped ventral one.

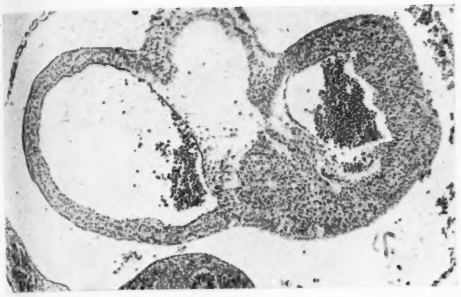
Figs. 2–10. These are all microphotographs of the septum primum in a 7·1-mm. embryo (× 124). The dorsal wall of the auricle is towards the top of the page. Fig. 2 shows that the dorsal myocardial proliferation has not quite reached the ventral end of the septum but is in contact with a small ventral outgrowth to the left of it. In the next section (fig. 3) the septum just fails to meet the ventral wall and in two sections below this last (fig. 4) contact is only maintained by some proliferating endocardium. The succeeding two sections (figs. 5 and 6) show no contact at all between the two outgrowths; this is the foramen secundum. In figs. 7 and 8 which represent the next section and the next but one below the last, contact is again made by the two outgrowths, but in the next alternate sections (figs. 9 and 10) the ventral proliferation is seen to gradually fail and the foramen primum thus begins.

PLATE III

Fig. 1. A section of the heart of a 17·5-mm. embryo (× 103) showing the dorsal outgrowth which forms the septum secundum. *S.II.d.* septum secundum; *S.I.* septum primum; *L.V.V.* left venous valve; *S.V.* sinus venosus.

Fig. 2. A section of the heart of a 17·5-mm. embryo (× 103) 34 sections below fig. 1, to show the commencement of a ventral outgrowth which will also form the septum secundum. *S.II.V.* septum secundum; *S.I.* septum primum; *R.V.V.* right venous valve; *L.V.V.* left venous valve; *S.int.* septum intermedium; *I.S.V.S.* intersepto-valvular space.

Fig. 3. A section of the heart of an 11·2-mm. embryo (× 103) to show the knoblike projection from the right side of the septum primum, *X*. *S.I.* septum primum; *R.V.V.* right venous valve; *L.V.V.* left venous valve; *S.int.* septum intermedium; *I.S.V.S.* intersepto-valvular space.



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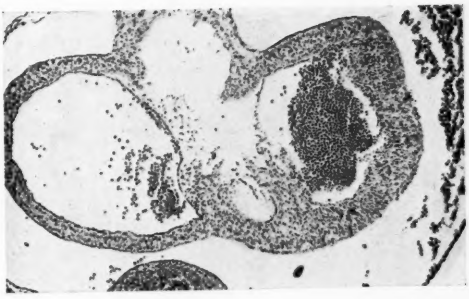

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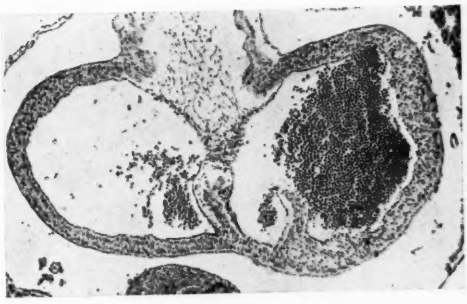

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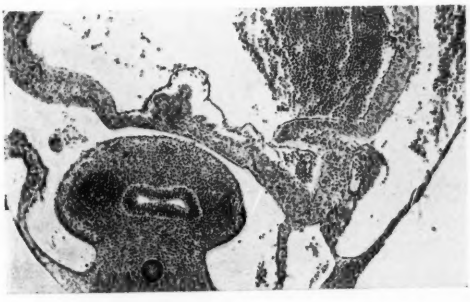

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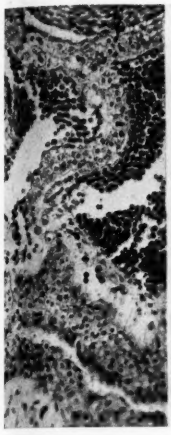

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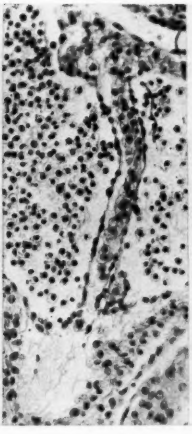

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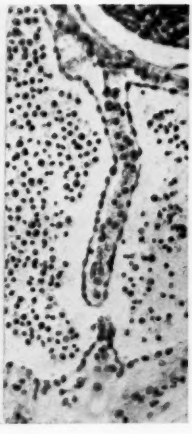

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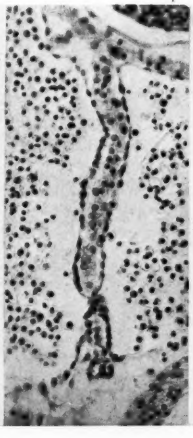

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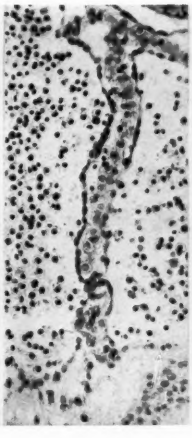

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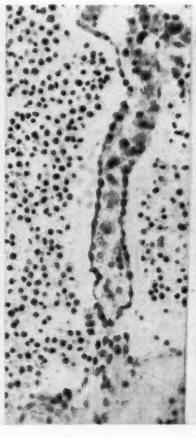

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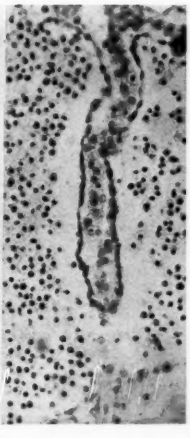

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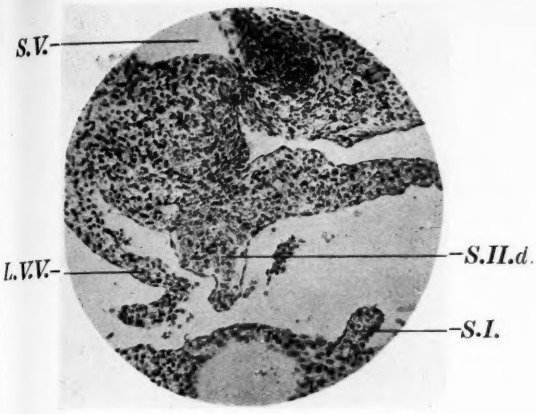

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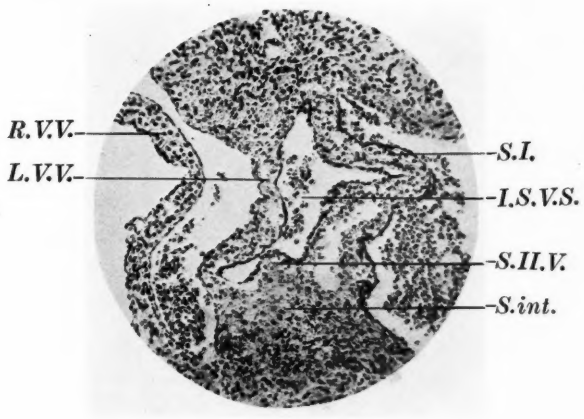

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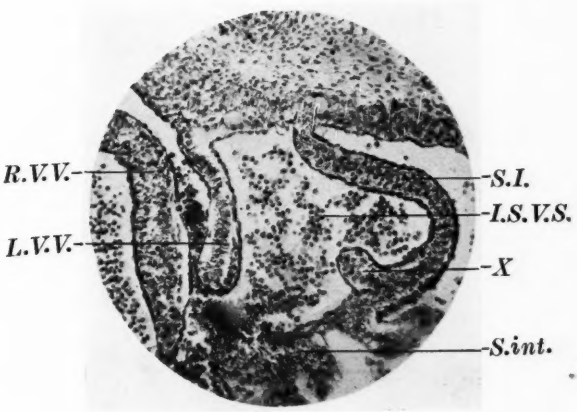

Fig. 3.

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A CASE OF CONGENITAL HEART DISEASE WITH SINGLE ARTERIAL TRUNK

By GEORGE DAVISON, M.B., B.S.

Cases of solitary arterial trunk appear to be sufficiently rare to warrant the recording of a single case.

The heart to be described was found in an infant of 14 days. Apparently healthy at birth, which was normal, the child continued at first to thrive, but on the 10th day it did not appear well and was brought into hospital where it died on the 14th day with symptoms pointing to an infective process. During life it showed no evidence of a heart lesion.

Autopsy was performed on 23 April, 1934. Apart from the heart lesion to be described, the only feature of note was an acute broncho-pneumonia.

DESCRIPTION OF THE HEART

The heart was situated normally and its pericardial surface was smooth and shining; it was a little enlarged, measuring 5 cm. from base to apex and 4 cm. transversely.

The two atria and their auricular appendages were well formed, but there was a widely patent secondary foramen ovale.

The tricuspid and mitral valves were well formed and healthy.

Two ventricles were present of approximately normal relative size, but they communicated through a defect in the base of the interventricular septum. This defect, approximately 8 mm. in diameter, was situated in the posterior part of the anterior half of the septum, immediately anterior to the attachment of the septal leaflet of the tricuspid valve. The free margin of the defect, concave upwards, was rounded and muscular.

From the base of the heart, instead of an aorta and pulmonary artery, arose a single large arterial trunk, situated in a rider position over the septal defect and arising equally from the two ventricles. The orifice of this vessel was of 27 mm. circumference and was guarded by three well-formed semi-lunar cusps, two anterior and one posterior. From the sinuses above the right and left anterior cusps arose respectively a right and left coronary artery. Arising from the left anterior surface of the arterial trunk, just above and to the right of the left coronary ostium, 1 cm. above the base of the left anterior cusp, was a vessel 4 mm. in diameter. This vessel passed upwards, to the left and backwards in apposition to the arterial trunk. Presumably it was the pulmonary artery but, owing to the absence of any clinical indication of heart disease, the pulmonary connections were severed in removing the heart before their im-

portance had been realised, so that the further course of this vessel was lost. Above the origin of this vessel the arterial trunk pursued the course of a normal aorta and gave off similar branches including a small vessel, presumably a ductus arteriosus, from the concavity of the arch. This vessel was patent only for a few millimetres. As it had been severed in the removal of the heart, its lower connection was lost.

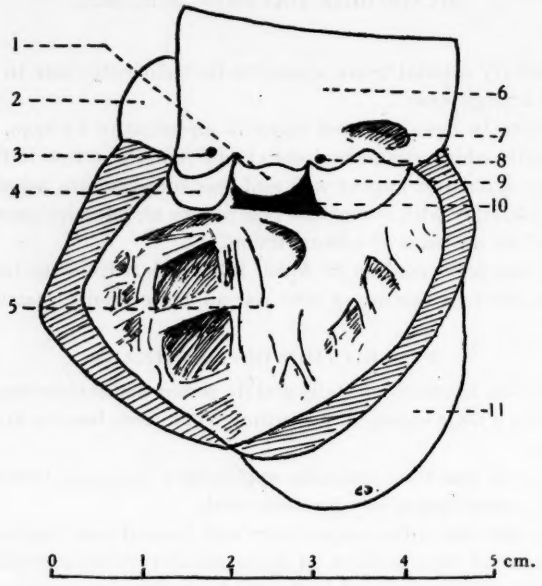

Fig. 1. (1) Posterior cusp. (2) Right auricle. (3) Right coronary. (4) Right anterior cusp. (5) Right ventricle opened. (6) Arterial trunk opened. (7) Pulmonary artery. (8) Left coronary. (9) Left anterior cusp. (10) Defect in interventricular septum. (11) Left ventricle.

The illustration shows the heart opened up by an incision into the right ventricle parallel to the septum and carried into the arterial trunk between the two anterior cusps. The specimen has been preserved and can be seen in the Pathological Museum of the Durham University College of Medicine.

DISCUSSION

In the heart which has been described there is an incomplete division into right and left sides, and by considering this in the light of embryological findings it may be possible to account for the appearances.

With regard to the atria, there is a widely patent foramen secundum, which must be the result of the secondary septum having failed to develop.

The defect in the ventricular septum is in that portion immediately below the semi-lunar cusps and anterior to the septal leaflet of the tricuspid valve, that is, embryologically, it is the proximal bulbar septum which is absent. The proximal bulbar ridges must, therefore, have failed to develop.

As regards the arterial trunk, we must bear in mind the following facts:

(1) The orifice is guarded by three well-formed semi-lunar cusps.

(2) The coronary ostia are normally situated with reference to these cusps.

(3) The pulmonary artery is given off just above the left anterior cusp.

(4) Above this opening the arterial trunk pursues the course and distribution of a normal aorta.

These can be accounted for most readily by assuming a partial persistence of the truncus arteriosus: we must assume that the aortic septum has developed incompletely, so that the aorta and pulmonary artery arise as a common trunk; on the other hand, the presence of three well-formed semi-lunar cusps argues that the division of the distal bulb has occurred, and that the pulmonary half has then undergone atresia. Were the case one of complete persistence of the truncus arteriosus one would expect to find its orifice guarded by four semi-lunar cusps, the coronary arteries arising from opposite sinuses. The two other types of single arterial trunk, truncus aorticus solitarius and truncus pulmonalis solitarius, in which it is presumed that normal division of the truncus arteriosus has occurred and that complete atresia of one stem has then ensued, can be excluded; in the case of complete truncus aorticus solitarius the pulmonary artery would not arise from the main vessel just above its origin, while in the case of truncus pulmonalis solitarius the coronaries arise abnormally.

LITERATURE

The rarity of this condition is confirmed by a study of the literature. Abbott (1) could collect but twenty-three cases of partial or complete persistence of the truncus arteriosus from the literature and other sources.

Humphreys (2), in an excellent review of the subject, records a case, gives a detailed account of the embryology, and gives criteria for distinguishing true persistent truncus arteriosus from the other varieties of solitary arterial trunk. She recognises only twenty cases of this defect; five of persistent common trunk with four semi-lunar cusps, three with three cusps and a rudimentary fourth, seven possible cases with only three cusps, and five doubtful cases with no recognisable sixth arch derivatives.

Shapiro (3) admits but two cases of true persistent truncus arteriosus. He states that this is the least common type of solitary trunk, while the most common is truncus aorticus solitarius.

A recent case is that described by Beaver (4) in which other congenital defects, including absence of one kidney, were observed.

SUMMARY

A case of congenital heart disease has been described, in which the following processes are presumed to have occurred:

(1) Failure to develop of the secondary atrial septum.

(2) Failure to develop of the proximal bulbar septum.

(3) Atresia of the pulmonary half of the distal part of the bulbus arteriosus.

(4) Incomplete development of the aortic septum.

These defects gave rise to no evidence during life, but death occurred on the fourteenth day from broncho-pneumonia.

The author is deeply indebted to Prof. R. B. Green of the Anatomy Department of Durham University for valuable advice and criticism.

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DEVELOPMENT AND HISTOGENESIS OF THE HUMAN PINEAL ORGAN

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INTRODUCTION

In the past and recently, the study of the pineal system has been approached from widely different standpoints, namely: (1) The morphological. (2) The ontogenetic and biological, with reference to certain problems, such as differentiation, including the association of change of function with correlated changes in form and structure; and questions pertaining to the persistence in living animals of organs which, in some remote palaeozoic epoch, have lost their primary function; also the occurrence of degenerative changes in such structures, and the fate of vestigial organs generally. (3) The clinical, which is intimately concerned with the physiology of endocrine organs, and the pathological, pharmaceutical and surgical aspects.

Owing to the vestigial condition of the pineal body in Man and Mammals generally, the study of the organ in these has hitherto not received the same minute attention that has been given to it in lower types of Vertebrates. Recently, however, the remarkable progress in diagnosis and treatment of tumours of the pineal gland has done much to focus attention on the structure and exact anatomical relations of the human epiphysis, and the practical application of this work has demonstrated the necessity for further detailed investigation.

A comparison of older with more recent literature on the subject shows that, although the pioneer and classical researches carried out by Dendy, Studnička and others on the pineal system of Fishes, Amphibia and Reptiles has left little of importance to be added, the later work, especially with regard to the development and histogenesis of the human pineal organ, notwithstanding improved technique in staining of special tissues and the details of cell structure, has left many fundamental points unsettled.

In this communication we shall endeavour to limit ourselves as far as possible to an account of our personal observations on the general development, histogenesis and adult structure of the human pineal gland, and we shall reserve

the consideration of the clinical aspect of the subject for a separate publication which will include the description of cases and their treatment, special points in the surgical anatomy of the pineal gland and the neighbouring blood vessels, and a general survey of the results obtained by experimental work on the function of the mammalian pineal gland.

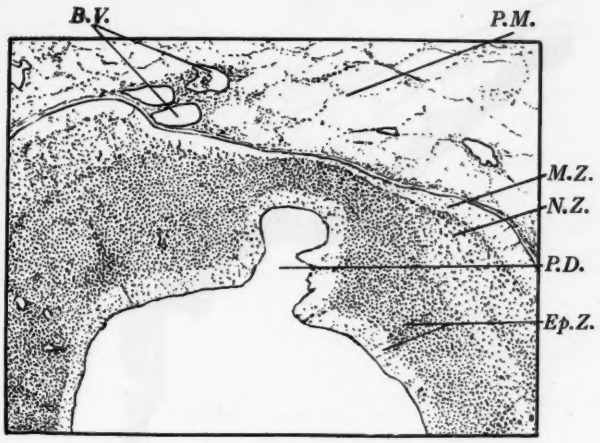
DEVELOPMENT OF THE HUMAN PINEAL ORGAN

An examination of the early human embryos in the Anatomical Department of King's College, London, indicates that the pineal organ of the human subject arises as a simple diverticulum from the roof of the third ventricle shortly after the 12-mm. stage of development, and that it is preceded by the formation of the posterior commissure. The earliest stage described by Krabbe was observed by him in a 15-mm. human embryo. In front of the pineal diverticulum was a solid mass of cells with spherical nuclei. This mass was directed forward. In addition to the posterior commissure there was a slight indication of the habenular commissure.

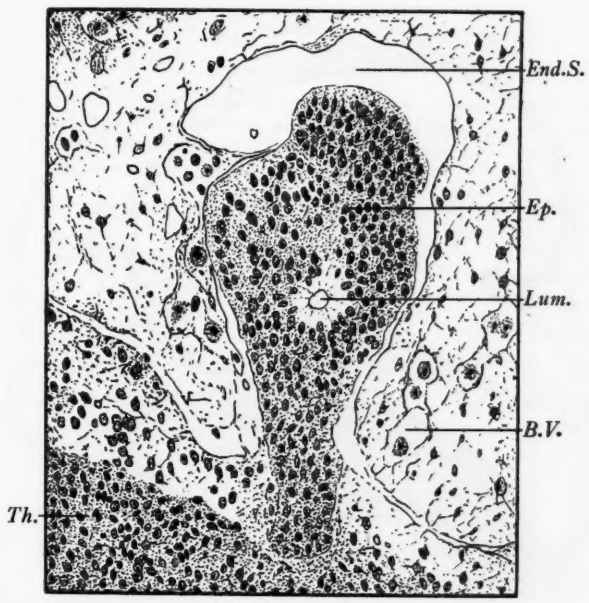
In a series of closely graded human embryos belonging to Prof. J. E. Frazer, which he has kindly permitted us to examine, the earliest stage in which a pineal diverticulum could be recognised was in a 15-mm. embryo; it appeared as a single median groove open towards the ventricle and situated in the posterior part of the roof of the thalamencephalon. It extended through fifty-four sections of approximately 10 μ thickness. Posteriorly the groove widened out, but in part of its extent the margins were in contact, and the appearance suggested that they were about to unite with each other, and in this way cut off a short tube, ending blindly in front and opening posteriorly into the third ventricle. A well-developed posterior commissure lay behind the pineal rudiment.

No pineal diverticulum was recognisable, with certainty, in the stages immediately preceding (14 mm.) and succeeding (16 mm.) the 15-mm. specimen just described. The organ was present, however, in a 17-mm. embryo and in succeeding stages.

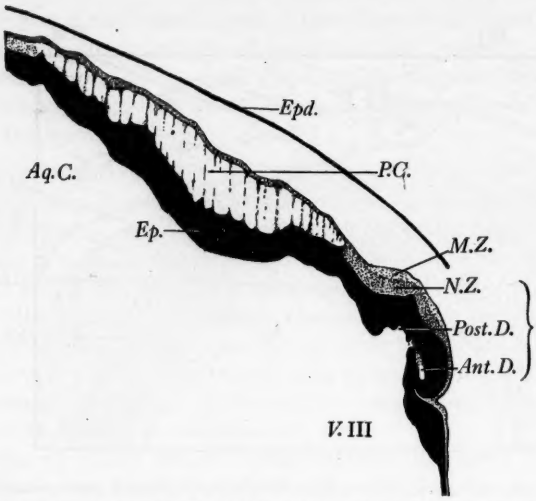
Among our own specimens there is a well-developed pineal diverticulum in a 19-mm. embryo and also in a 20-mm. embryo ($7\frac{1}{2}$ weeks); the latter was sectioned coronally, and thus the plane of the sections was transverse with respect to the brain. In this embryo (text-figs. 1, 2, 3) the pineal organ consists of a posterior hollow diverticulum (text-fig. 1), the lumen of which is in wide communication with the cavity of the third ventricle, and an anterior part, the apex of which is directed forward and which contains a central lumen (text-figs. 2 and 3). This lumen is not actually continuous with that of the posterior part, but there is an intermediate segment in which one sees a radial arrangement of the central cells around a virtual lumen. The general form and position of the organ, with the apex directed forward, closely resembles that which is present in the corresponding stage of development in other Mammals, e.g. the rabbit (text-fig. 4), in Birds (text-fig. 5), in Reptiles (text-fig. 6), in Amphibia (text-figs. 7, 17), and in Fishes.



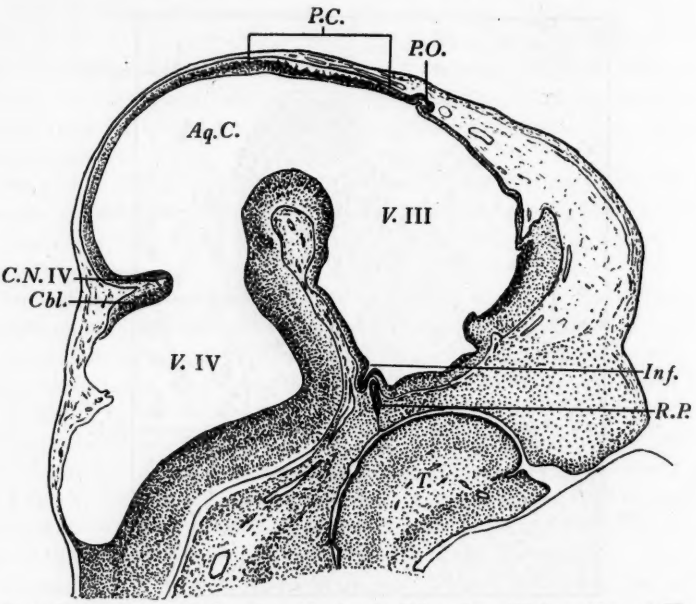
Text-fig. 1. Pineal evagination, 20 mm. Human embryo. The section passes transversely through the posterior part of the diverticulum, where its lumen is continuous with the cavity of the third ventricle.



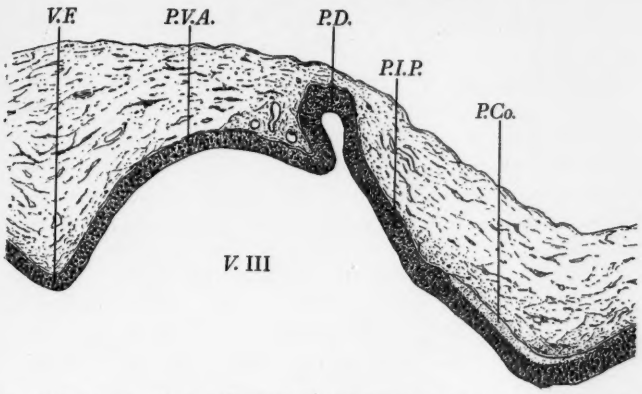
Text-fig. 2. Pineal organ of the same embryo as text-fig. 1. The section passes transversely through the anterior part of the organ, and shows the central lumen surrounded by radially arranged ependymal cells.



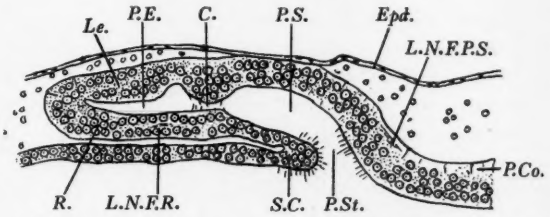
Text-fig. 3. Median linear reconstruction of the pineal region and posterior commissure of the same embryo, transverse sections of which are shown in text-figs. 1 and 2. The apex of the pineal diverticulum is directed forward.



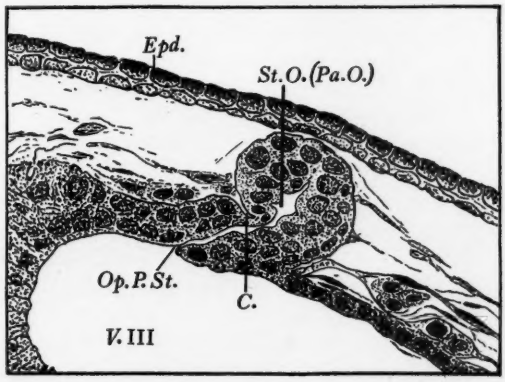
Text-fig. 4. Median longitudinal section of brain of rabbit embryo (16 days, 11 mm.). The apex of the pineal body is directed forward, and the diverticulum shows a central constriction which partially divides it into an anterior and posterior lobe (compare text-figs. 3, 6 and 7).



Text-fig. 5. Median longitudinal section of the pineal diverticulum of a chick embryo (fourth day). The apex is directed forward.



Text-fig. 6. Semi-diagrammatic representation of a medial longitudinal section of an embryo *Sphenodon*, showing a constriction marking off the anterior (left) lobe, or "parietal organ", from the posterior (right) lobe or "pineal sac". The anterior end of the organ is directed forward and is to the left in the figure (after A. Dendy).



Text-fig. 7. Median longitudinal section of the pineal diverticulum of a frog tadpole, showing a constriction in the plane of the cranial capsule, which indicates the future line of separation of the "parietal organ" (Stieda) from the "epiphysis" or "pineal sac". The apex of the organ is directed forward, and is to the right in the figure.

The wall of the diverticulum consists of all three zones of the neural tube, ependymal, mantle and marginal. The ependymal cells are arranged radially round the lumen of the diverticulum (text-fig. 2), and some of their nuclei show mitotic figures. This layer may therefore be regarded as a proliferating zone of ependymal cells, from which newly formed cells migrate outward into the mantle layer. Externally is a thin reticular or marginal zone. This is in relation with the outer covering of pia mater and mesenchyme, in which a plexus of thin-walled capillary vessels forms a conspicuous feature (text-fig. 2).

A median linear reconstruction of the region (text-fig. 3) shows the general appearance of the organ at this stage, and also its relation to the posterior commissure, which is now well developed and extends backward for a considerable distance in the roof of the aqueductus cerebri. The general extent of the commissure at this stage of development is well seen in text-fig. 4, which is drawn from a median section through the brain of a rabbit embryo, and text-fig. 5, from a fourth day chick embryo. Plate I A shows the concentration of the fibres of the posterior commissure into a round transverse bundle which commonly takes place at a later stage of development, exemplified in an 8-day chick embryo. A paramedial section (text-fig. 8) of the same rabbit embryo as text-fig. 4 shows the connections and general ventro-caudal direction of the fibres of the posterior commissure as they course backward to the pons, and also fibres passing to the interpeduncular region.

The next stage of development that we shall describe is that seen in a 22-mm. human embryo, obtained at operation by Mr E. McClellan to whom we are also indebted for valuable help in the construction of the wax model, a drawing of which is shown in Plate II D. The model represents a portion of the mid-brain and thalamencephalon magnified 50 diameters. It has been divided into right and left halves by a median sagittal section.

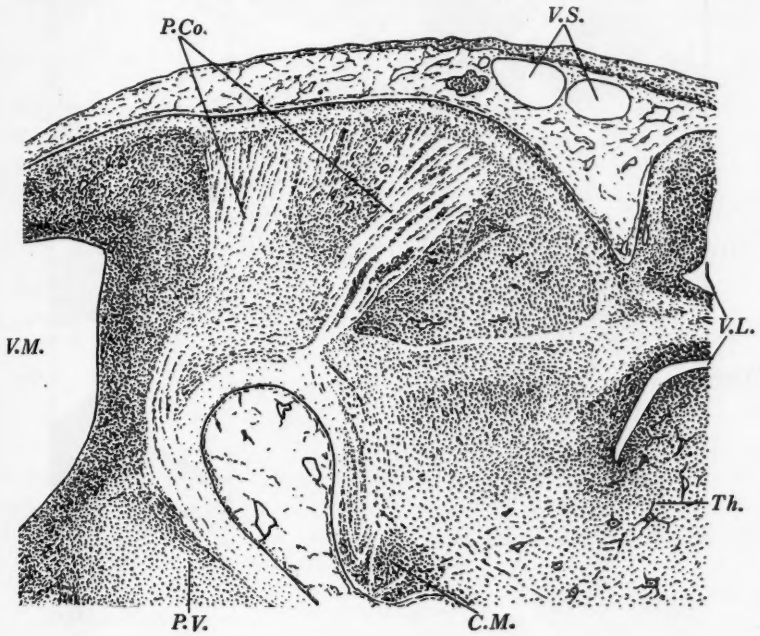
From behind forward the median section of the model (Plate II D) shows a portion of the roof of the aqueductus cerebri, the posterior commissure, and the posterior intercalary plate. The roof of the aqueduct shows a longitudinal median groove and two small pockets produced by thickened bands of the posterior commissure giving rise to a transverse folding of the ependyma. These infrapineal recesses are temporary in nature and will disappear later when the upper part of the intercalary plate is folded backward round the posterior commissure, to form with the commissure a transverse projecting bar between the upper end of the aqueduct and the recessus pinealis. In front of and dorsal to the posterior commissure is a posterior median diverticulum (Plate II B, C, D).

In front of this is an anterior bilobed diverticulum (Plate II B, D). The wall of both the posterior and anterior diverticulum is formed by the whole thickness of the neural tube.

A solid mass of neuro-epithelial cells lies in front of the anterior diverticulum, and appears to have arisen as an outgrowth from its anterior wall. It

is partially subdivided into right and left halves by a median fissure, and extends downwards as a flattened band from near the apex to the base of the diverticulum.

Anterior to the two pineal diverticula is an ependymal diverticulum (Plate II A, D), the dorsal or posterior extremity of which is bilobed. The opening of the cavity of this ependymal outgrowth into the third ventricle is to the right of the median plane. Its dorsal wall is directly continuous with the ependymal roof of the third ventricle, and it corresponds to the "dorsal

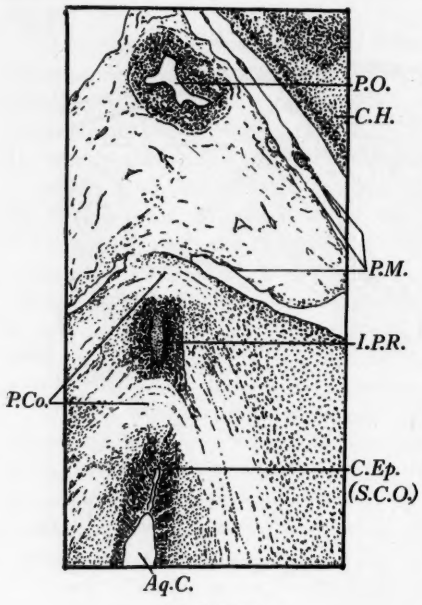


Text-fig. 8. Paramedian section through the mid-brain of a rabbit embryo (18 days), showing the direction of the fibres of the posterior commissure and their connections with the pons Varolii and interpeduncular region.

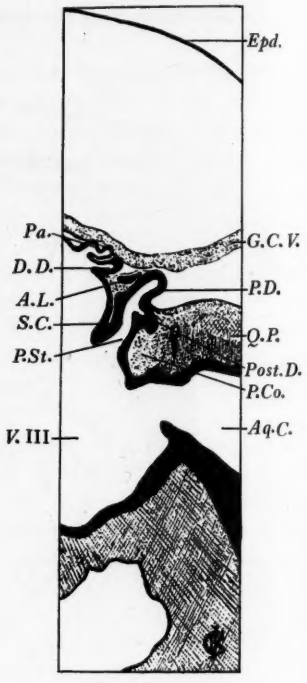
sac" of the reptilian brain. In the human foetus it persists as the "dorsal" or suprapineal diverticulum, which is represented in the adult by the small suprapineal recess.

It is probable that the anterior pineal diverticulum seen at this stage of development corresponds to the main part of the definitive pineal gland and gives rise to the "posterior lobe" of Krabbe, while the solid mass of neuro-epithelial cells in relation to its anterior wall represents the "anterior lobe" of Krabbe. The posterior diverticulum seems to persist for a time as the infrapineal recess which is present in the 6-cm. stage (text-fig. 10).

If the pineal region be examined at a much later stage of development, e.g. a 6-cm. human embryo, it will be found that the pineal organ has increased considerably in size. Its lumen still communicates with the cavity of the third ventricle, where it opens between the habenular commissure in front and the posterior commissure behind. The long axis of the organ appears to have been rotated backward round a transverse axis passing through its base; so that



Text-fig. 9.



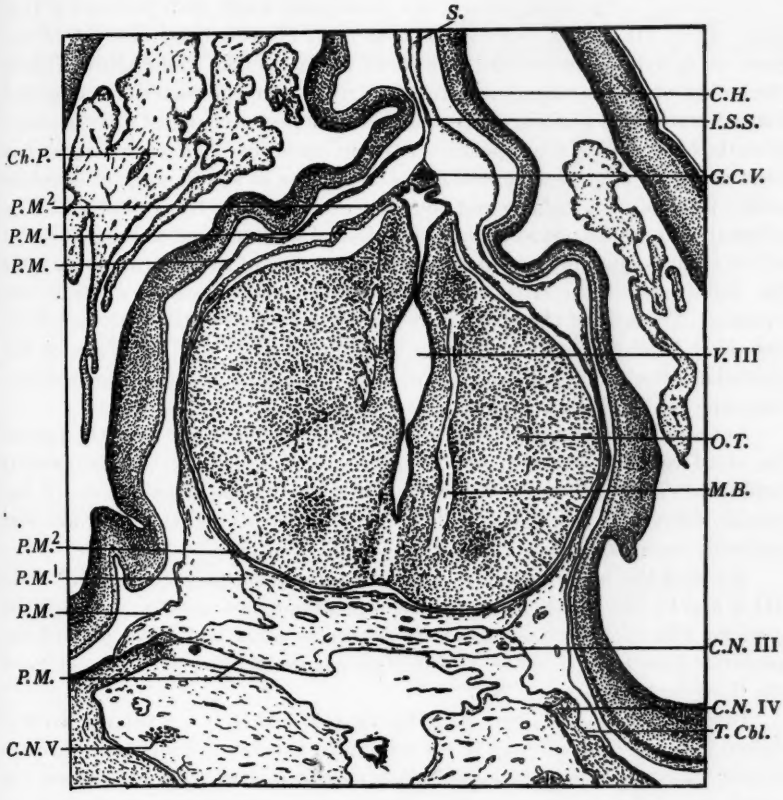
Text-fig. 10.

Text-fig. 9. Transverse section through the pineal organ of a human embryo (6 cm.) showing its relations to the membranes, posterior commissure and subcommissural organ.

Text-fig. 10. A median linear reconstruction of the pineal region of a human embryo (6 cm.) showing the main diverticulum, infrapineal recess, anterior lobe, superior and posterior commissures, the dorsal sac, and an anterior diverticulum possibly representing a vestige of the paraphysis; also the great cerebral vein and opening of the aqueductus cerebri.

the apex of the organ, which in the early stages of development was directed forward, now projects upward and backward (text-fig. 10). It lies below the great cerebral vein (text-fig. 10, *G.C.V.*) and primitive falx cerebri, and above the superior quadrigeminal plate of the mid-brain (text-fig. 10, *Q.P.*). It is contained in a triangular space bounded below by the roof plate of the neural tube and the layer of pia mater which invests the brain stem, and laterally by

right and left membranous laminae, which are attached above to the lower border of the interhemispheric septum or primary falx cerebri. Along the line of junction of the lateral laminae with the lower edge of the interhemispheric septum is a membranous channel which encloses the great cerebral vein (text-



Text-fig. 11. Transverse section through the posterior thalamic region of a human embryo (6 cm.) showing the relation of the cerebral membranes to the great cerebral vein and neural tube at the junction of the lateral plate with the dorsal lamina, and the extreme thinness of the membrane (lower part of interhemispheric septum) which joins the sheath of the great cerebral vein to the lower margin of the falx cerebri.

fig. 11). At a later stage of development when the corpus callosum and fornix grow backward over the thalamencephalon and mid-brain, the thin lower part of the interhemispheric septum disappears (text-fig. 11, *S.*), while the upper and thicker part persists as the definitive falx cerebri, the inferior sagittal sinus (text-fig. 11, *I.S.S.*) being developed in its lower border. The septum in the

earlier stages of development is much thicker than at the stage described and is formed by a median condensation of the loose mesenchyme which occupies the space between the developing hemispheres. It is not formed by the union of the two layers of a fold, and the same remark applies to the formation of the tentorium and falx cerebelli.

Returning to the description of the pineal body itself, there is found at this stage (Plate III A, *A.L.*) an almost solid mass of cells, lying in front of the main or anterior diverticulum and above the habenular commissure. This is the anterior lobe. A recess projecting backward from the posterior wall of the main diverticulum probably corresponds to the posterior pineal diverticulum, described in the preceding specimen (22-mm. embryo). This pocket which has been described as the infrapineal recess disappears at a later stage of development, probably by opening out into the cavity of the third ventricle. The original stalk of the pineal diverticulum thus disappears and the pineal recess of the adult is probably a remnant of the basal part of the central cavity after the distal part of the latter has become closed and separated off from the ventricle. The wall of the apical part of the epiphysis and the anterior lobe is definitely lobulated at this stage, outgrowing finger-shaped processes of the epithelial diverticulum interdigitating with vascular ingrowths from the surrounding pia arachnoid.

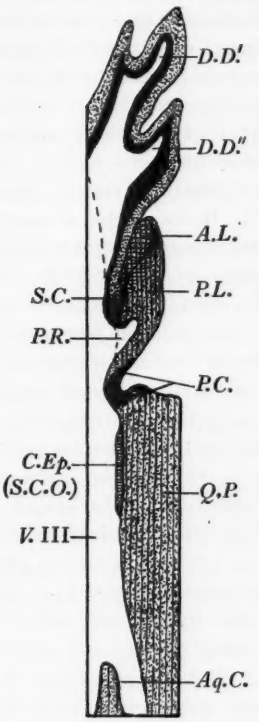
Anterior to the pineal diverticulum are two evaginations from the roof of the third ventricle (text-fig. 10). The apices of these outgrowths are directed backward. The more posterior overlaps the base of the anterior lobe of the pineal body, and represents the dorsal sac of Reptiles, while the anterior probably corresponds to the paraphysis of the Reptiles.

Between the fourth and fifth months of foetal life (text-fig. 12 and Plate III B and C) the distal part of the main posterior lobe and the whole of the anterior lobe of the pineal gland are solid; the stalk and basal part of the posterior lobe are still hollow and in wide communication with the cavity of the third ventricle.

Dorsal to the pineal organ (text-fig. 12, *D.D.'*, *D.D.''*) is a tubular diverticulum from the posterior part of the roof of the third ventricle. This bifurcates behind into two secondary lobes, which extend a short distance beyond the distal end of the pineal organ. The diverticulum is lined internally by a single layer of cubical epithelium, which in many places is invaginated into the lumen of the diverticulum to form a superficial secreting layer of epithelium covering tufts of choroidal villi. If the upper or dorsal wall of the diverticulum is traced forward, it is found to be directly continuous with the choroid plexus of the third ventricle, and since the habenular commissure lies behind the opening of the diverticulum between this and the stalk of the pineal body, it corresponds to the "dorsal sac" of lower Vertebrates.

If the solid "glandular" part of the pineal organ be examined at this stage of development (Plate III B, C, D), it will be seen that both the anterior and posterior lobes consist of a lobulated mass of neuro-epithelial cells, which is

penetrated by thin-walled vessels surrounded by loose perivascular sheaths. The epithelial cells are mostly derived from the inner ependymal zone of the diverticulum, but there are also a certain number of cells belonging to the nuclear or mantle zone, which may be distinguished by their position and by being less deeply stained than the ependymal cells, also by their nuclei being vesicular and pale in colour as contrasted with the deeply stained nuclei of the ependymal cells. At the periphery of the gland, branched finger-shaped or club-shaped processes of the epithelial cells grow outward into the surrounding



Text-fig. 12. Median linear reconstruction of the pineal region of a 4½ months' human foetus showing anterior opening of aqueductus cerebri; the columnar epithelium of the subcommissural organ between this and the posterior commissure, above which is the pineal organ consisting of a main posterior lobe which in the greater part of its extent is solid and a small anterior lobe. Above and in front of the pineal recess is the superior commissure and above this the bifid dorsal diverticulum.

pial tissue, and interdigitate with vascular processes which grow inwards between the epithelial cords (Plate III B, C, D). Further, if cross-sections of the interdigitating processes are observed, it will be seen that the vascular processes of pial tissue appear paler than the surrounding zones of epithelial cells; these vascular mesenchymal areas are limited where they come into contact with the neural epithelium by the external limiting membrane, between which and the zone of deeply stained cells derived from the ependyma are a few sparsely scattered pale cells belonging to the mantle zone. The general arrangement of the epithelial tubes or cords, and their relation to the ingrowing

vascular processes, is seen with diagrammatic clearness in Plate IV B and D, photographed from a section of the "pineal sac" of an adult *Sphenodon*.[1]

Should the cross-section of a vascular ingrowth of pial tissue be taken as the centre of an *apparent lobule*, this will be seen to consist of a core of sinusoidal blood vessels surrounded by a perivascular sheath of pial tissue, which is in contact peripherally with the external limiting membrane of outgrowing neuro-epithelial processes. Proceeding farther outward from the central pale area formed by the vessels and their loose mesenchymatous sheath, there will be found beyond the limiting membrane the reticular and nuclear zones, the latter containing pale cells with vesicular nuclei, and finally a peripheral zone consisting of deeply stained ependymal cells.

The deeply stained cells surrounding the clear areas have the appearance of epithelial cords cut in various directions. When the section is transverse (Plate IV F), the cords appear as rings of cells, "rosettes", with deeply stained oval nuclei arranged radially round a palely stained central zone, which is formed by the inner ends of the cells coming into contact in the central axis of the cord. If the section is longitudinal, two parallel rows of nuclei are seen, which are separated by a palely stained axial zone where the inner ends of the cells come into contact in the situation of a virtual lumen. These cords of proliferating ependymal cells are usually grouped in lobules which grow outward between the vascular ingrowths of the pia mater.

There is thus an appearance, produced by cross-sections of the cords, of groups of deeply stained epithelial cells arranged in "ring-like" zones or "rosettes". These surround the vascular ingrowths, which appear pale. This arrangement of alternating series of branched epithelial and vascular cords is the key to the "mosaic" appearance which is described by Globus and Silbert as characteristic of later stages of foetal life. The "streams" of deeply stained epithelial cells described by these authors are longitudinal sections of the epithelial cords. The central parts of the clear areas of the "mosaic" pattern are transverse or oblique sections through the ingrowing vascular processes, surrounded by pale cells with vesicular nuclei.

Owing to the radial disposition of the epithelial cells around a central axis which is destitute of nuclei, the general appearance of a group of epithelial cords, cut transversely, is similar to that of an acinar gland, but with the important difference that in the human subject the acini usually have no lumen and no ducts are present. In the early stages of development of the pineal organ in some Birds (Plate I A and B), the main epithelial outgrowths are at first hollow and in communication with a principal duct, which corresponds to the lumen of the primary diverticulum and opens into the cavity of the third ventricle. In these Birds, therefore, the primary condition of the pineal organ

[1] This specimen is from one of the series of microscopical sections illustrating the development of the pineal region of *Sphenodon* and *Geotria* which were prepared by the late Prof. Dendy, and we take this opportunity of thanking Prof. D. Mackinnon for permission to make use of this most valuable collection in our present investigation.

shows a complete correspondence to that of an acino-tubular gland; but since in the later stages of development the acini become cut off as hollow vesicles from the duct system, and these vesicles eventually lose their central cavity, it is clear that the difference between the mammalian and avian pineal organ is one of degree rather than of kind, and that the organ in both is built up on essentially the same plan.

Even in the early stages of foetal development in the human subject, the original arrangement of interdigitating epithelial and vascular processes becomes obscured, especially in the centre of the developing organ. This is partly due to degeneration and gradual disappearance of many of the vascular sinuses which form the central structures in the pale areas, and partly to the appearance of cells with pale vesicular nuclei in the tissue between the central core of vascular mesenchyme and the small deeply stained cells. These pale cells are derived from the proliferating deeply stained cords of epithelial cells, and are comparable with the cells of the nuclear or mantle zone of the developing neural tube elsewhere, which are differentiated from the germinal or inner layer of proliferating ependymal cells.

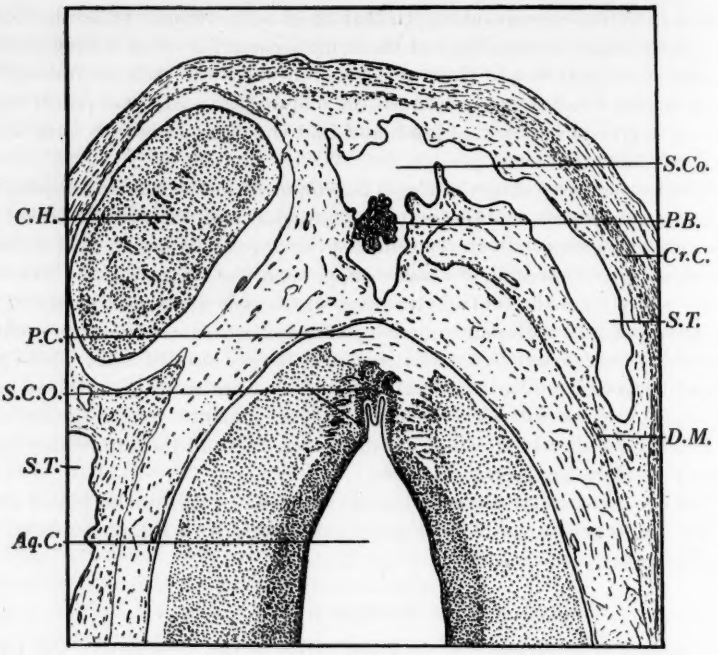
The later post-natal stages of the development of the human pineal organ will be considered in the following section dealing with the structure of the pineal gland.

STRUCTURE OF THE PINEAL GLAND

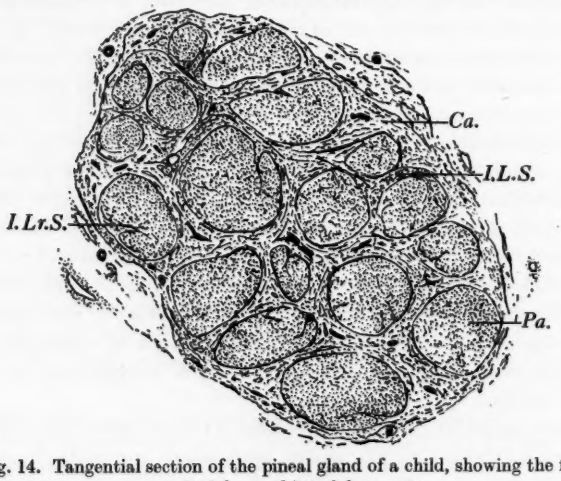
A considerable amount of variation exists in the structure of the pineal gland at different age periods and in different individuals. These changes have recently been specially investigated by Globus and Silbert, who have worked on human material ranging from a 5½ months' foetus to old age, and these authors consider that the variability in the structure of tumours arising in the pineal region, either from the pineal body itself or from "rests" in the vicinity of the organ, may be explained on the assumption that the tumour tissue assumes the character in some cases of one age period of its development, and in others of another age period.

Besides variations in structure due to age changes, there are differences in appearance which are brought out by different methods of preparation, and we propose, before dealing with the selective actions produced by the use of special methods of modern technique, to give a short description of the microscopic appearance of a section of the pineal gland of a child of five years of age, stained by the ordinary haematoxylin and eosin method. We shall then endeavour to interpret the appearances seen at this stage of development and in the adult organ by a reference to the earlier stages of embryonic and foetal development, and by the microscopic pictures brought out by the use of differential stains.

The pineal gland at this stage (text-fig. 14) is invested by a fibro-vascular capsule derived from the pia mater, and lined internally by a neuroglial stratum. This capsule sends trabeculae containing blood vessels into the sub-



Text-fig. 13. Transverse section through the pineal region of a rabbit embryo (18 days) showing the intimate relation of the fundus of the pineal body to the venous sinuses, where the great cerebral vein joins the plexus at the sinus confluens, and the relation of the fibres of the posterior commissure to the subcommissural organ and ependyma.



Text-fig. 14. Tangential section of the pineal gland of a child, showing the fibrous capsule, lobes and interlobar septa.

stance of the gland. The trabeculae pass inward between and partially surround the peripheral part of a branched system of lobules which originate from the neuro-epithelium of the primary pineal diverticulum. The lobular areas between the trabeculae communicate with each other in the central part of the gland, so that the lobules are not completely enclosed in separate compartments but are continuous with a central mass of parenchymatous tissue which is more uniform in appearance than the lobulated peripheral zone. The lobules consist of a supporting glial tissue which has the character of a fibrillated sponge-work or reticulum enclosing clear intercommunicating spaces. Some of the spaces contain parenchyma cells with vesicular nuclei, while others appear empty. The reticulum is especially noticeable beneath the capsule and in relation with the larger trabeculae. The cell elements of the reticulum have the appearance of being continuous with each other, no intercellular septa ever being visible. The network thus seems to be formed of a plasmodium or spongioplasm within which the nuclei of the cell elements are imbedded. In many of the spaces of the network, however, as stated previously, branched parenchyma cells containing pale vesicular nuclei are present. The processes of these cells may be:

(1) Continuous with the processes of similar adjacent cells.

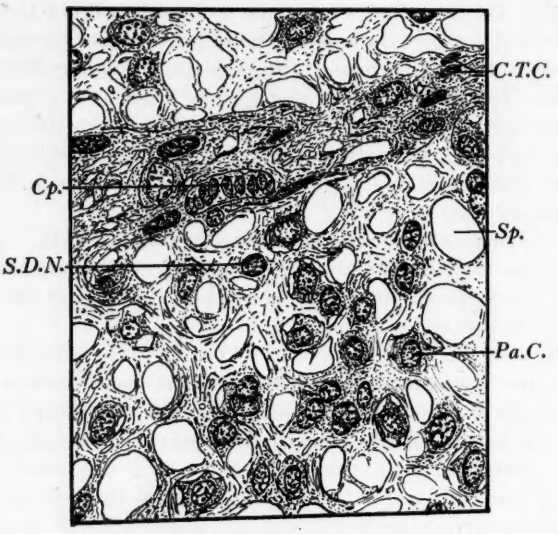
(2) Continuous with the matrix of the general neurospongium.

(3) They may spread out on the perivascular sheaths of the vessels contained in the trabeculae or fibrous capsule.

The cells with the pale vesicular nuclei belong to the fully developed type of "pineal" or "parenchyma" cell, and both the nuclei and cytoplasm may contain granules or spherules, which are believed by Dimitrowa and others to be secretory in nature. Many of the parenchyma cells, however, are imbedded in the neurospongium, and in this situation the nucleus is usually smaller and more deeply and uniformly stained than those of the cells just described. Between these two extreme types, both in young and adult specimens, there are numerous intermediate forms (text-fig. 15), both with respect to the type of the nucleus and the position of the cell element, namely, wholly contained within the neurospongium, protruding from this into a space, or completely extruded into the space, and connected with the surrounding structures merely by fine tapering processes.

In adult specimens specifically stained for neuroglia, the distinction between "neuroglia cells" and the general plasmodium or syncytial reticulum in which they are imbedded is quite definite, and it is at once evident that the slender neuroglia cells and neuroglial fibres in no sense form the principal constituent of the supporting tissue of the lobules. The former appear as very sparsely scattered branched cells, chiefly of the "astrocyte" type, with fine delicate processes lying in a tissue which is principally composed of branched parenchyma cells which form what appears to be a continuous reticulum. This reticulum is permeated by a fine capillary network, and a delicate plexus of thin-walled vessels with their connective tissue sheaths. The fibro-vascular

elements are, however, quite inconspicuous, and the branched parenchyma cells form the bulk of the lobular tissue. The proportion that the supporting tissue bears to the fully developed parenchyma cells varies in different specimens. In some there are large tracts of dense finely fibrillated tissue, which either replace the lobular parenchymal tissue in certain parts of the gland, or may penetrate into its substance and thus break it up into small lobules, separated by interlobular septa. This tissue is described as "glial" or "fibroglial", and contains a varying proportion of neuroglial cells, neuroglial fibres, and fibrous connective tissue surrounding blood vessels.



Text-fig. 15. Section of an adult pineal gland stained by van Gieson's method and eosin, showing the apparent continuity of the reticulum in which the parenchyma cells are imbedded; and also the relation of the parenchyma cells to the spaces of the reticulum and the supporting tissue or neurospongium. An interlobular septum showing capillary blood vessels and nuclei of fibrous connective tissue crosses the upper part of the drawing obliquely. The tissue of the interlobular septum appears to be directly continuous with the neurospongium.

An excessive development of fibroglial tracts and septa occurring in old subjects appears to be an indication of degeneration. The trabecular tissue of the developing organ, in which the vessels with their connective tissue sheaths are imbedded, appears to be largely derived from the primary undifferentiated neurosyncytium, and a balance of power seems to be established between the differentiation and growth of parenchyma cells, and the limiting influence of the fibroglial trabeculae which surround them. The variations in the proportion of parenchyma cells to supporting trabecular tissue, which occurs even in young subjects, may perhaps be explained on the hypothesis that the organ,

being vestigial in nature, the power to differentiate parenchyma cells and to maintain their existence is less in some subjects than in others.

The arrangement of the cell elements of the lobules is very irregular, but occasionally an alveolar appearance is present in pineal glands at this period of growth, namely 4–5 years, or even in adult specimens which is similar to that seen in foetal life and at birth (Plate IV F). This affords an indication of the original developmental structure, namely, the outgrowth of proliferating cords of epithelial cells from the germinal or ependymal layer of the primary diverticulum, which alternate with ingrowing vascular processes of the pia mater (see p. 437). In specimens stained by van Gieson's method, the interlobular and intralobular fibrous connective tissue, in the substance of the gland, does not show the characteristic pink coloration which is strictly limited to the external fibrous capsule and some of the main trabeculae. It seems, therefore, that the chemical constitution of the intralobular connective tissue is altered in some way by contact with the secretion or tissue fluid contained in the spaces, and does not take on the specific staining reaction that it would do otherwise.

The "parenchymatous" cells with pale vesicular nuclei which occupy the spaces of the reticulum appear to have a position relative to the reticulum which corresponds to the position of nerve cells relative to the supporting glial tissue in the brain and spinal cord.

Both the parenchymatous and the true neuroglial cells of the pineal gland seem to be differentiated from the indifferent cell elements of the primary neurosyncytium, much in the same way as, in the central nervous system, neuroblasts and spongioblasts are developed from undifferentiated parent cells of the primary neurosyncytium of the brain and spinal cord. In the human subject, however, the process of differentiation does not appear to proceed so far as in either the "pineal sac" (epiphysis) or in the "retina" of the pineal eye of Reptiles and cyclostomes. In these, definite "sensory" and ganglion cells are present which were first described by Studnička, Dendy, Gisi, Hoffmann, and others, who demonstrated that in the retina of the pineal eye they are normally present and are related to nerve fibres.

The typical parenchyma cells of the mammalian pineal organ seem to be intermediate in character between the "indifferent cell", which is the parent of the neuroblast, and the fully developed nerve cell. The occasional "neuronoid", "sensory" and true "ganglion" cells, which do not belong to the sympathetic system and which have been observed in the human pineal organ by various authors, might, on this hypothesis, be regarded as cells which under abnormal conditions have completed their full development as nerve cells, whereas the typical parenchyma cells, though undoubtedly arising from neuroblastic tissue, have been transformed during phylogeny into a type of cell which differs from both neuroglial and nerve cells in containing what are apparently secretory granules, and in the absence of an axis cylinder.

NERVE SUPPLY OF THE MAMMALIAN PINEAL ORGAN

We do not propose in this communication to discuss the general question of the nervous supply of the pineal apparatus, and we shall simply allude to our observations on the nerve supply of the human pineal gland. We have seen in specimens stained by Blair and Davies' modification of Ranson's method, plexuses of fine non-medullated fibres and small ganglion cells belonging to the sympathetic system, distributed along the course of the vessels entering and leaving the gland and around the parenchymatous cells. Non-medullated nerve fibres and cells were also present in the membranes surrounding the pineal gland and at or near its posterior extremity. These correspond to the plexus described by Cajal in the rat, the nervus conari described by Kohlmer, and the retropineal ganglion of Pastori discovered by him in the dog.

We have also seen bundles of medullated nerve fibres in specimens stained by osmic acid passing between the superior and posterior commissures and the parenchymatous tissue at the base of the gland where they diverge and appear to be distributed between the cell elements; but we have not been able to determine their exact mode of termination, nor have we seen any true ganglionic nerve cells with an axis cylinder process. We have, however, encountered a few large cells of a "neuronoid" type, but these resemble aberrant forms of pineal cells rather than true nerve cells.

Our examination of the pineal system of lower Vertebrates and a study of the very extensive literature on the subject has led us to the belief that with the exception of the sympathetic nerves and cells, which are associated with the blood vessels entering and leaving the gland, the nerve supply of the adult mammalian pineal organ, like the organ itself, is tending to become vestigial. Even in lower classes of vertebrate animals, the pineal nerves which were present in early embryonic stages have often completely disappeared in the later stages of embryonic or larval life. This is especially the case when the "parietal organ" or "terminal vesicle", as in the frog tadpole (text-fig. 17), or the "pineal sac" in the mouse embryo becomes separated by a considerable distance from its primary site of origin from the neural tube. The literature bearing upon the nerve supply of the pineal system is voluminous, and the following references are mentioned merely with the object of indicating some of the more important contributions to the subject. Spencer, B., in 1886, first described the parietal nerve in *Varanus giganteus*: Darkschewitsch, 1886; Béraneck, 1892; Studnička, 1893; Klinckoström, 1894; Cajal, 1895; Dendy, 1899–1911; Gaskell, 1908, 1910; Krabbe, 1916; Horrax, 1927; Herring, 1927; Pastori, 1928, 1929; Rio Hortega, 1932.

The full complement of nerve fibres and associated ganglia which it may be assumed should be developed in connection with the pineal system, is probably never present in any one type of animal, for in the course of time, the organ has undergone fundamental changes in form, and presumably also of function. These changes have accompanied its evolution in certain lower

types of Vertebrates, and its regression or degeneration in many Mammals. The nerve supply of the organ has naturally participated in these changes!

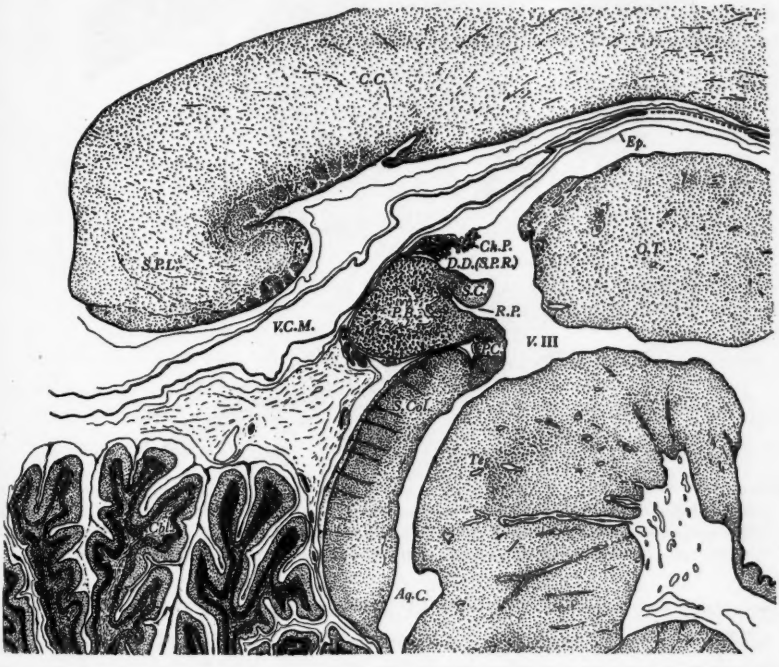
The nerve fibres which one might expect to be present in a fully evolved pineal system, fall into the following categories:

(1) Somatic afferent, from pineal sensory cells to central nervous system.

(2) Somatic efferent, from central nervous system to the pineal organ or accessory structures connected with it.

(3) Visceral afferent, from pineal organ to sympathetic ganglion.

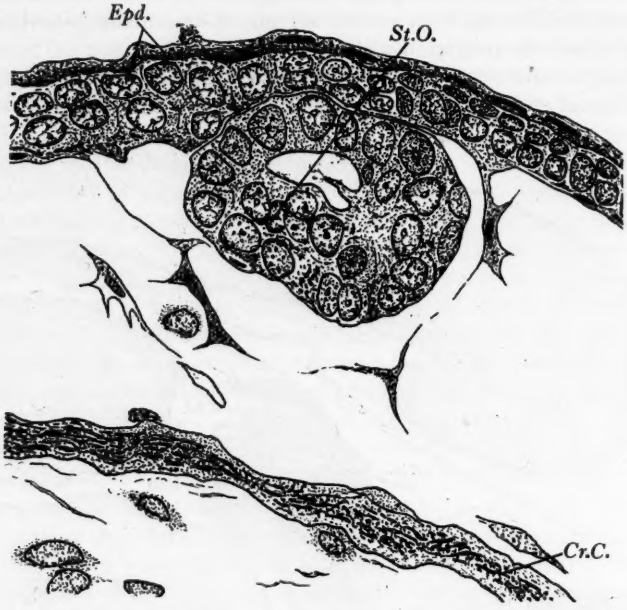
(4) Visceral efferent, from sympathetic ganglia to pineal organ.



Text-fig. 16. Drawing of a medial longitudinal section through the pineal region of a human subject showing the relations of the pineal organ to the corpus callosum, fornix, great cerebral vein, dorsal diverticulum, and chorioid plexus, superior and posterior commissures, quadrigeminal plate, and the membranes and blood vessels at its posterior pole.

There is abundant evidence in Fishes, Amphibia and Reptiles of nerve fibres, passing between sensory cells of the "retina" of the "pineal eye" and the central nervous system, which it is presumed are afferent to the habenular and other ganglia. In the human subject, medullated nerve fibres connect the anterior and posterior commissures with the parenchyma of the pineal organ, but there seems to be no reliable evidence of the direction of the nerve impulses which traverse these fibres.

It is probable that the sympathetic nerves which accompany the vessels entering and leaving the mammalian pineal gland, and connect it with the retropineal ganglion and plexus on the great cerebral vein, function as sympathetic nerves elsewhere and are both afferent and efferent.



Text-fig. 17. Section through Stieda's organ of a frog tadpole, at a later stage of development than that shown in text-fig. 7. The terminal vesicle (parietal organ) is completely cut off from the epiphysis, and careful search through sections behind the vesicle failed to reveal any nerve tract or remnant of the original connection between it and the "epiphysis" or brain.

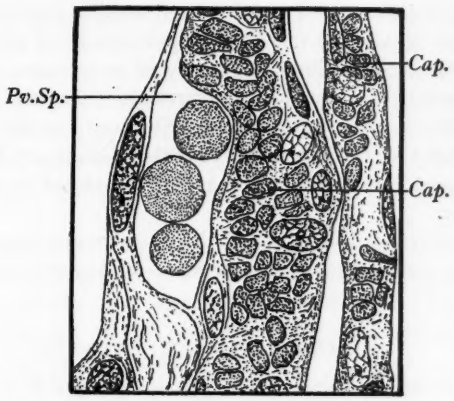
CORPORA ARENACEA

The presence of corpora arenacea in the pineal glands of young as well as old subjects may be regarded as additional evidence of degenerative changes taking place in a vestigial organ. We do not propose to discuss here their mode of formation further than to mention incidentally that they appear to arise in the first instance by the coalescence of minute droplets of a finely granular material, deposited in pericapillary tissue spaces (text-fig. 18).

PINEAL CYSTS

The presence of glial tracts and plaques is of considerable practical importance in connection with the development of cysts. These seem to be most frequently due to the breaking down of the central part of a glial area and the accumulation of tissue fluid in the spaces thus formed. They are often quite

irregular in their disposition, and the larger cysts are apparently formed by the coalescence of smaller spaces. A good example of such a cyst is shown in Plates VI A and V C. The specimen was found in a brain in the Anatomy Department, King's College, London. No history could be obtained. The wall of the cyst was lined by condensed glial tissue, and no ependymal cells were visible in any of the sections. These were cut serially, and as no epithelial cells were found in the lumen it is probable that their absence could not be accounted for by the epithelium being shed into the cavity of the cyst. Some of the cells forming the immediate lining of typical cysts may be swollen up and rounded, giving a false impression of their nature; these cells must be regarded as pseudo-epithelial, and not in typical cases as being ependymal. The cavum pineale usually disappears early, and though cases have been described in



Text-fig. 18. Section through a perivascular space in an adult human pineal organ showing minute droplets of a finely granular material probably of a colloid nature and indicating an early stage in the formation of a corpus arenaceum.

which remnants of it have persisted in infants and even in adults the majority of cysts met with in the pineal glands of adults appear to be due to the breaking down of the central parts of glial areas, which areas have themselves arisen by a regressive degeneration of localised portions of the parenchyma. If the cysts were due to persistence of portions of the original cavity of the pineal diverticulum one would expect them to be more frequent in the pineal glands of infants and young children than at puberty or in the adult, and they would tend to lie in the central axis of the organ and be regular in their general disposition. They are, however, more frequently found in subjects from the period of puberty onwards, and are often quite irregular in their disposition.

The origin of pineal cysts has been studied by a considerable number of workers, of whom special mention may be made of Krabbe, Marburg and Cooper. These authors have all contributed valuable information on this

difficult subject and agree in describing the frequent presence of glial plaques and extreme variability in structure of the pineal gland at different ages. Their interpretation, however, of the appearances found more especially with respect to the lining of the cyst wall by ependymal cells and the formation of the glial plaques differs in certain essential points from what we have described. The evidence of the specimens which we have examined justifies the conclusion that in a large proportion of specimens, with the exception of the pineal recess, the cavity of the primary pineal diverticulum has disappeared completely in young infants and at birth, and also that in one specimen, from a 4½ months' foetus (Plate III B and C, and text-fig. 12) the greater part of the pineal organ was solid, and only the stalk of the diverticulum was hollow.

Cysts lined by ependyma and containing villi are probably derived from the dorsal diverticulum (Plates V E, F and VI A), portions of which may become cut off and persist as closed vesicles. They may be distinguished from the typical pineal cysts by the absence of a peripheral zone of glial tissue outside the pseudo-epithelium which lines the cavity of an ordinary pineal cyst. As a rule only the peduncle of the dorsal diverticulum persists in the adult. It forms the suprapineal recess, which, as is well known, varies considerably in size, but usually has the relations shown in text-fig. 16, where it is seen wedged in between the great cerebral vein above and the pineal gland and superior commissure below.

Dermoid and teratomatous cysts of the pineal region may also be easily distinguished from pineal cysts by the presence of skin and by the contents of the cavity.

SUMMARY AND CONCLUSIONS

1. The pineal organ of Mammals and Birds is derived from a diverticulum, the form and the site of origin of which, between the anterior and posterior commissures, corresponds closely to that of the primary pineal diverticula of Reptiles, Amphibia and Fishes.

2. The apex of the primary pineal diverticulum is at first directed forward in all classes of Vertebrates.

3. The definitive position of the pineal organ in the human subject with the apex directed backward is largely due to mechanical causes, such as the backward growth of the splenium of the corpus callosum and fornix.

4. In the early stages of development of the membranes of the brain, the lower border of the primary interhemispheric septum contains a large vessel which is the precursor of the great cerebral vein and straight sinus. This is continued back into the sinus confluens. At a later stage when the corpus callosum and fornix grow backward above the thalamencephalon and midbrain, this primary vessel is joined by a new vessel, the inferior sagittal sinus. This is developed in the lower border of a thickening of the upper part of the primary septum which becomes the falx cerebri, whereas the thin lower part of the septum in front of the tentorium cerebelli disappears.

5. Between the third and fifth months of foetal life there occurs an active proliferation of neuro-epithelial cells derived from the inner or ependymal zone of the pineal diverticulum. These grow outward in the form of cords, the component cells of which are arranged radially round a central axis which is destitute of nuclei. This is accompanied by a simultaneous ingrowth of vascular processes of mesenchyme.

6. A special mass of proliferating cells growing from the anterior wall of the main diverticulum gives rise to the solid anterior lobe of Krabbe, whereas the cords growing from the fundus of the diverticulum form the principal solid part of the posterior lobe. The stalk and posterior diverticulum (infrapineal recess) probably open out, and their lumina become incorporated in the cavity of the third ventricle, whereas the cavity of the main or anterior diverticulum, which may be cut off as the "cavum pineale", usually disappears.

7. The neuro-epithelial cells give rise to the glia lining the fibrous capsule and covering the trabeculae, the parenchyma cells and the neuroglial cells (astrocytes). The ingrowing vascular mesenchyme forms the fibrous capsule and the connective tissue basis of the septa and finer trabeculae including the contained vessels. Many of the sinusoidal vessels in the central part of the pale vascular areas seen in the earlier stages of development disappear, leaving only a very fine capillary plexus in the parenchymatous tissue of the lobules.

8. The parenchymatous tissue in the adult consists of a reticulum of "branched" pineal cells, among which are a few neuroglial cells chiefly of the "astrocyte" type. The "alveolar" appearance which is sometimes seen in adult specimens is due to the persistence of primary neuro-epithelial cords, cross-sections of which appear as "rosettes".

9. The frequent appearance of glial tracts or plaques containing scattered remnants of degenerating parenchymal cells is an indication of the vestigial condition of the pineal organ in the human subject, and these plaques afford an explanation of the liability of the pineal gland to undergo cystic degeneration, and possibly also the origin in it of certain types of tumour.

10. Pineal cysts may result from the breaking down of the central areas of glial plaques. The nuclei of the glial tissue next the lumen of the cyst may give rise to the appearance of a pseudo-epithelium (compare Plate IV D with Plate V D).

11. Cells and nerve fibres belonging to the sympathetic system accompany the vessels entering and leaving the pineal organ, and medullated nerve fibres connect the anterior and posterior commissures with the parenchymatous tissue.

True ganglion cells belonging to the central nervous system and having an axis cylinder process, although described by some authors, appear to be very rarely seen in the human pineal gland. Transitional forms exist, which are intermediate between the large cells described as "neuronoid" and "parenchyma" cells.

ABBREVIATIONS

A.B.D.	Anterior bilobed diverticulum.
Ant.D.	Anterior diverticulum.
A.L.	Anterior lobe.
Aq.C.	Aqueductus cerebri.
B.V.	Blood vessel.
C.	Constriction between "pineal sac" and "pineal eye".
Ca.	Capsule.
Cap.	Capillary.
Cav.	Cavity.
Cbl.	Cerebellum.
C.C.	Corpus callosum.
C.E., C.Ep.	Columnar epithelium.
C.H.	Cerebral hemisphere.
Ch.P.	Chorioid plexus.
Ch.P.V. III	Chorioid plexus of third ventricle.
Ch.P.L.V.	Chorioid plexus of lateral ventricle.
C.M.	Corpus mammillaris.
C.N. III	Cranial nerve III.
C.N. IV	Cranial nerve IV.
C.N. V	Cranial nerve V.
Cp.	Capillary.
C.T.	Connective tissue.
C.T.C.	Connective tissue cells.
Cr.C.	Cranial capsule.
Cyst.	Cyst containing chorioidal villi.
C.V.	Chorioidal villi.
D.D., D.D.', D.D.''	Dorsal diverticulum and its subdivisions.
D.S.	Dorsal sac.
D.M.	Dura mater.
E.L.M.	External limiting membrane.
End.S.	Endothelial space.
Ep.	Ependyma.
Ep.D.	Ependymal diverticulum (dorsal sac).
Epd.	Epidermis.
Ep.Z.	Ependymal zone.
Ep.C.	Epithelial column.
F.C.	Vessels in fibrous capsule.
F.F'.	Fornix.
G.C.V.	Great cerebral vein (Galen).
Gli., G.Sh.	Glial sheath.
Gl.St.	Glial stratum (pseudo-epithelium).
H.G.	Habenular ganglion.
I.S.S.	Inferior sagittal sinus.
I.L.S.	Interlobar septum.
I.Lr.S.	Interlobular septum.
Inf.	Infundibulum.
I.P.R.	Infrapineal recess.
L.	Lobule.
Le.	Lens.
L.N.F.P.S.	Layer of nerve fibres of pineal sac.
L.N.F.R.	Layer of nerve fibres of retina.
Lum.	Lumen.
M.B.	Meynert's bundle.
M.Z.	Marginal zone.
N.Z.	Nuclear zone.

Op.P.St.	Opening of pineal stalk.
O.T.	Optic thalamus.
P.	Pulvinar.
Pa.	? Paraphysis.
Pa.C.	Parenchyma cell.
Pa.O.	Parietal organ (pineal eye).
Par.	Parenchyma.
P.B.	Pineal body.
P.C.	Pineal cells.
P.Co., *P.C.*, *P.C.*^{1}, *P.C.*^{2}	Posterior commissure.
P.Cyst.	Pineal cyst.
P.D.	Pineal diverticulum.
P.E.	Pineal eye (parietal organ).
P.I.P.	Posterior-intercalary plate.
P.L.	Posterior lobe.
P.M., *P.M.*^{1}, *P.M.*^{2}	Pia mater.
P.M.D.	Posterior median diverticulum.
P.O.	Pineal organ.
Post.D.	Posterior diverticulum.
P.P.O.	Peduncle of pineal organ.
P.R.	Pineal recess.
Pr.Ep.	Epithelial process.
P.S.	Pineal sac.
P.Sh.	Pial sheath.
P.St.	Pineal stalk.
P.V.	Pons Varolii.
P.V.A.	Post-velar arch.
Pv.Sp.	Perivascular space.
Q.P.	Quadrigeminal plate.
R.	Retina.
Ros.	"Rosettes".
R.P.	Rathke's pouch.
S.	Septum interhemispheric um.
S.C.	Superior commissure (habenular commissure).
S.C.O.	Subcommissural organ.
S.Co.	Sinus confluens.
S.Col.	Superior colliculus.
S.D.	Secondary diverticulum.
S.E.	Secondary evagination.
S.D.N.	Small darkly stained nucleus.
Sp.	Space.
S.P.L.	Splenium.
S.T.	Sinus transversus.
St.O.	Stieda's organ (terminal vesicle).
Sub.ep.	Subependymal layer.
T.	Tongue.
T.Cbl.	Tentorium cerebelli.
Th.	Thalamus.
Teg.	Tegmentum.
Thr.	Thrombus.
V.C.M.	Great cerebral vein (V.M. Galeni).
V.C.T.	Vascular connective tissue.
V.F.	Velar fold.
V.M.	Ventriculus mesencephalicus.
V.L.	Ventriculus lateralis.
V. III	Third ventricle.
V. IV	Fourth ventricle.
V.S.	Venous sinuses.

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* A comprehensive bibliography of the literature on the Pineal System, including its pathological and clinical aspects, will be found in the references marked with an asterisk.

EXPLANATION OF PLATES I–VI

Plate I

A. Medial longitudinal section of the pineal region of a chick embryo (8 days), showing the main pineal diverticulum, and secondary diverticula, which have arisen as hollow outgrowths from the former; also the relation of the superior and posterior commissures to the stalk of the main diverticulum, and the dorsal sac.

B. Oblique coronal section of pineal organ of a chick embryo, of the same age as the preceding, showing the primary and secondary diverticula, and some fibres of the posterior commissure.

Plate II

Transverse sections of pineal region of a 22-mm. human embryo and median aspect of the right half of a model reconstructed from the corresponding series of sections.

A. Section through the posterior bifurcated end of the anterior ependymal diverticulum, in the plane A of the model.

B. Section through the anterior bilobed diverticulum, and posterior median diverticulum, in the plane B of the model.

C. Section through the posterior median diverticulum and posterior commissure in the plane C of the model.

D. Drawing of the median aspect of the right half of the model showing the relations of the superior and posterior commissures to the pineal diverticula.

Plate III

Transverse sections of the pineal region of a 6-cm. human embryo, and of a 4½ months' foetus.

A. Section through the basal part of the main pineal diverticulum of a 6-cm. human embryo showing, in the upper part of the photograph, the solid anterior lobe. Below this is the main pineal diverticulum, the wall of which shows proliferating cords of ependymal cells growing outward, into the surrounding tissue. Below the pineal evagination is a section through the infrapineal recess, the epithelial lining of which is assuming a columnar type. Fibres of the posterior commissure are seen at the sides and below the pineal region.

B. Coronal section through the pineal region of a 4½ months' human foetus showing the relation of the dorsal diverticulum (suprapineal recess) to the pineal gland. Clusters of elongated chorioidal villi project into the lumen of the diverticulum. The pineal gland shows partial subdivision into an anterior and posterior lobe.

C. The pineal gland more highly magnified showing the ingrowth of vascular processes of the pia mater between the outgrowing neuro-epithelial cords.

D. Peripheral portion of the gland ×55 D., showing pale areas containing a central core of vascular pia mater, alternating with dark zones, composed of neuro-epithelial cords.

PLATE IV

A. Transverse section through the distal end of the pineal evagination of a 6-cm. human embryo. It shows folding of the wall of the diverticulum and outgrowth of the proliferating ependymal cells into the mantle zone.

B. Section through the pineal region of an adult *Sphenodon* (Dendy collection), showing in the upper part of the photograph the pineal evagination, the wall of which is folded in a manner similar to the human, but the extension of the lumen of the diverticulum into the outgrowing processes is much more pronounced. Below and to the right of the photograph are seen sections of portions of the paraphysis and dorsal sac.

C. Transverse section through the basal part of the pineal evagination of the 4½ months' human foetus, seen in Plate III B, C and D, showing outgrowth of neuro-epithelial cords, more especially from the anterior aspect and sides of the tube; on the posterior aspect (below in photograph) the epithelium is differentiating into the columnar type, characteristic of the subcommissural organ.

D. Detail of B, × 139 D., showing in the centre a pseudo-lobule, with its central core of vascular pia mater, between two hollow neuro-epithelial outgrowths.

E. Section through the subcapsular part of a pineal gland of an infant (1 year, 4 months), showing the fibrous capsule and the penetration of a blood vessel into the substance of the gland. The vessel is surrounded by a perivascular sheath of fibrous connective tissue, outside which is a glial sheath, the cellular and fibrous components of which are continuous with the neurospongium which forms the supporting tissue of the lobules and contains the parenchyma cells.

F. Portion of the same specimen × 261 D., showing the predominance at this stage of the cells with small dark nuclei, and the arrangement of the cells in cords which when cut in cross-section are seen to be disposed radially round a central core which is destitute of nuclei, giving the acinar appearance sometimes described as "rosettes".

PLATE V

A. Section through an adult human pineal gland showing the parenchymatous tissue on the right and on the left a tract of glial tissue, characterised by sparsely scattered small oval nuclei imbedded in a reticulum of glial fibres.

B. Section through a glial plaque from the same specimen, × 194 D.

C. Section through the wall of the pineal cyst shown in A, Plate VI. The lumen of the cyst is below and it is seen to be lined by condensed glial tissue, no ependymal epithelium being visible. Compare with the ependymal epithelium shown in Plate IV C.

The middle zone is formed of a degenerate tissue containing few parenchyma cells, and showing numerous spaces. In the upper part of the section is the fibrous capsule containing blood vessels with thickened walls.

D. Section through a thrombosed vessel in a pineal tumour. The endothelium lining the vessel is destroyed on the left side, and the vessel is surrounded by a small cell infiltration. The thrombus contains a large proportion of leucocytes.

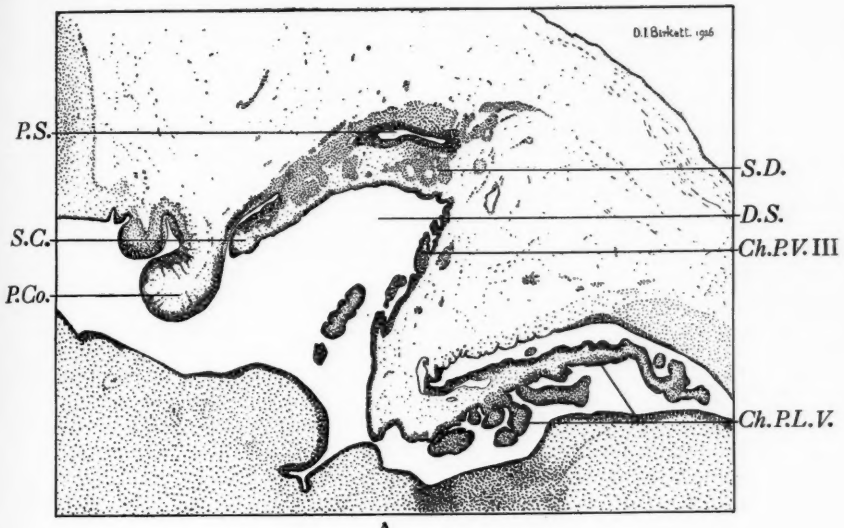
E. Portion of the wall of the dorsal diverticulum lying above the pineal cyst shown in Plate VI A, showing chorioidal villi and corpora arenacea.

F. Section through a cyst lying outside the parenchymatous tissue of a pineal tumour. The cyst is lined by ependyma and chorioidal villi project into its lumen. A corpus arenaceum is imbedded in its wall.

PLATE VI

A. Section of pineal cyst shown in Plate V C and E. The drawing also shows the relation of the dorsal diverticulum to the pineal gland, and chorioidal villi projecting into its lumen. Corpora arenacea are present in the tissue surrounding the pineal cyst and the diverticulum, and are also imbedded in their walls.

B. Section of pineal tumour showing the lobulated arrangement of the tumour tissue, and tracts of degenerating glial tissue, containing thin-walled blood vessels.



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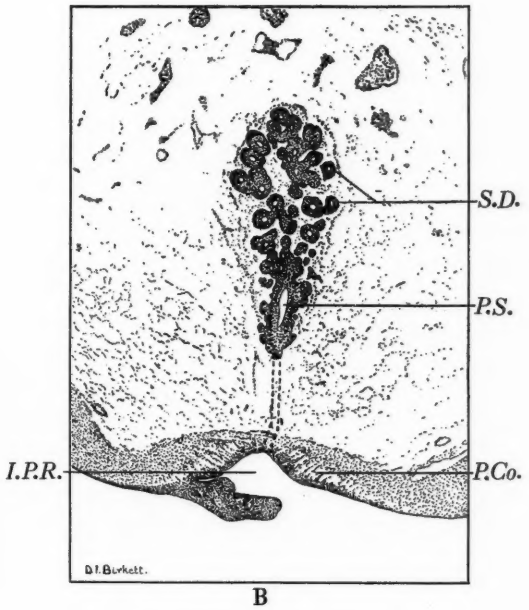

B

GLADSTONE AND WAKELEY—THE HUMAN PINEAL ORGAN

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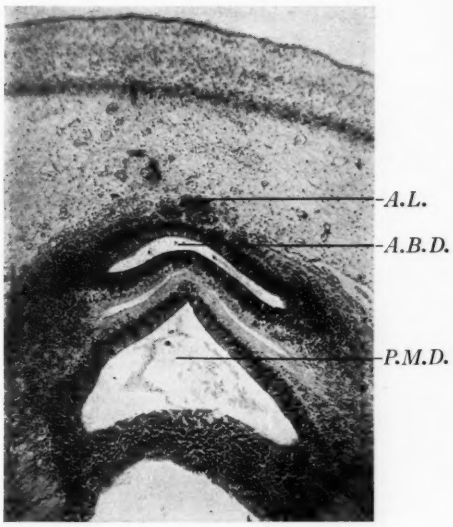

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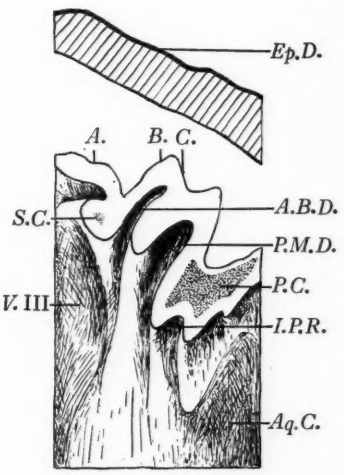

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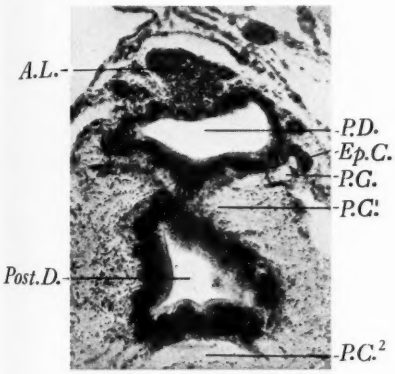

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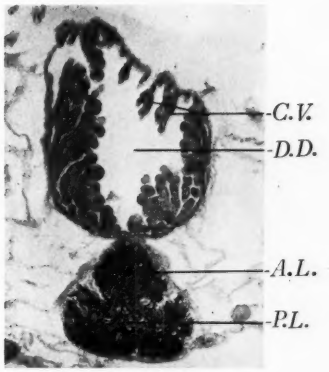

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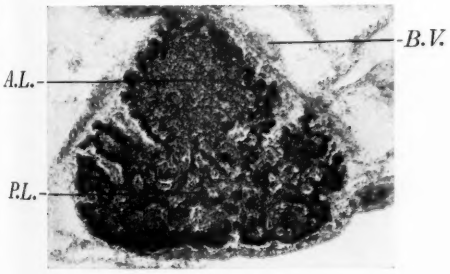

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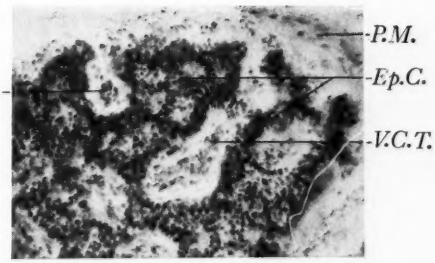

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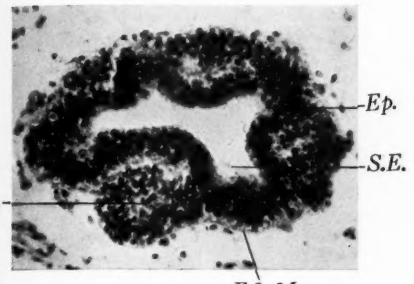

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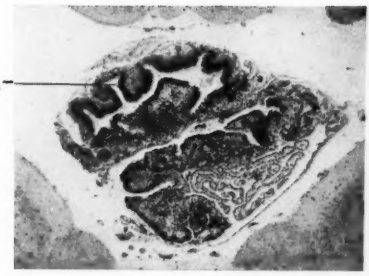

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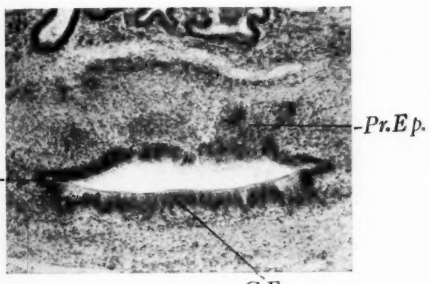

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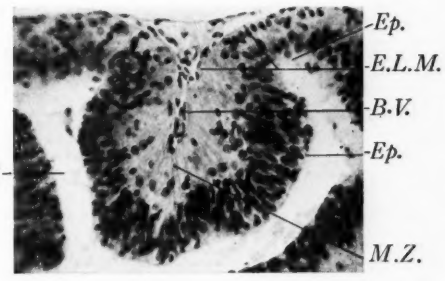

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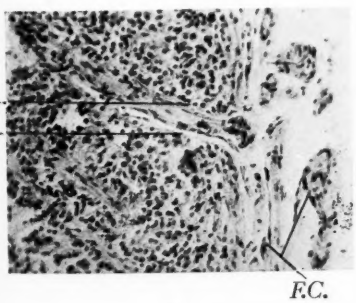

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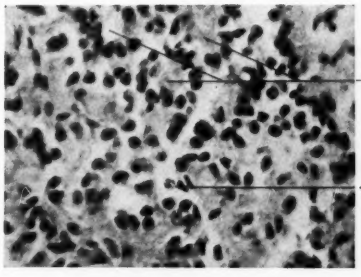

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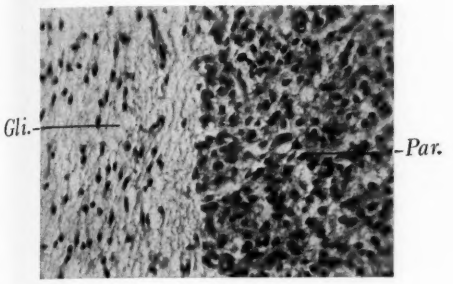

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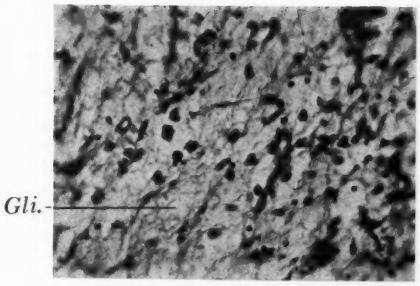

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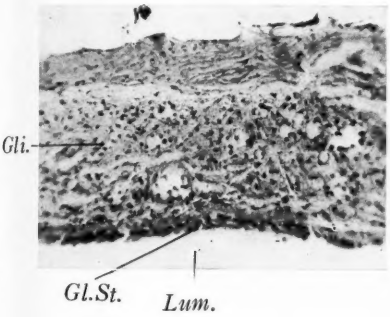

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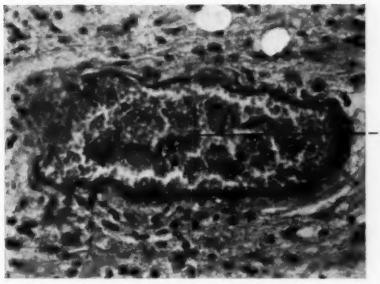

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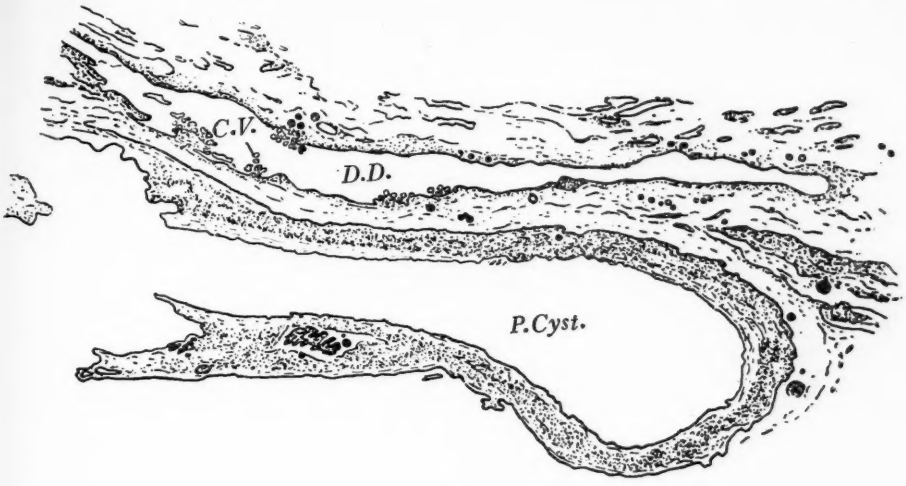

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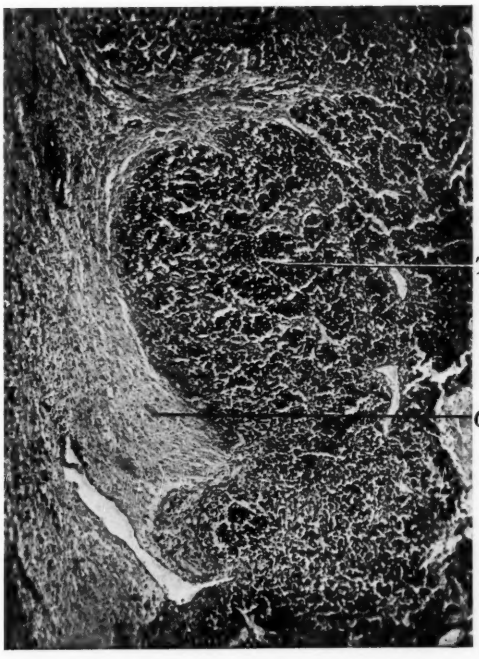

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THE TERMINAL PART OF THE WOLFFIAN DUCT

By J. ERNEST FRAZER, *London*

It is a matter of common knowledge that the caudal end of the Wolffian duct is concerned in some way with the formation of the bladder, and that in the course of the changes taking place the ureter comes to end separately in that viscus, while the opening of the duct finally is into the prostatic urethra. Nevertheless, although these facts are recognised, there does not seem to be any settled or accepted view concerning the way in which the changes actually take place: in a very general way it is said that the Wolffian duct is "taken up" into the bladder, or is "expanded" as far as its ureteric opening, while the apparent change of site of its own opening is usually left without even an attempt at a definite explanation. In this paper I propose to give the result of an enquiry into these matters. A few years ago I indicated the way in which the actual final opening is produced, and the present is a more complete account of observations then shortly recorded, with addition of the earlier changes.

There are actually two parts or stages in the process, that in which the duct disappears as far as the ureteric implantation, and that which brings about the change in level of its aperture. The two stages, although making a continuous whole in their progress in time, are sufficiently distinguished—by their objectives on the one hand, and by the regions of the duct involved on the other hand—to justify the separation in description. The second stage follows immediately on the first. The changes which take place in the Wolffian ducts progress quickly, and individual variations, although quite noticeable at times, are simply the results of temporary differences in the speed at which the changes are effected.

The Wolffian duct, just before its ureteric bud begins its growth, is shown in fig. 1, a semi-schematic drawing from an embryo of 4·9 mm. The duct is seen running down the lateral aspect of the Wolffian body (*WB*), but, as it nears the caudal part of this ridge, it crosses it obliquely, over its ventral aspect, and then loops forward to reach the cloaca. In doing this the duct lies in close contact with the mesoderm of the ridge, on its ventral side, as is shown in the upper of the two smaller figures. This is from the 4·9 mm. specimen, in which there is no indication of the ureteric bud, but in the lower figure—from a 5 mm. specimen—the beginning bud is shown: it arises in actual contact with its metanephric cap, from this part of the duct, springing from its dorsal and somewhat medial aspect.

Evidently, then, it is that part of the duct extending between this ureteric point and the cloaca which disappears to allow the ureter to open into the

bladder, while the portion of duct immediately cranial to the point is that which is concerned in making the final opening.

The conditions present in the embryo of 4·9 mm. are shown in fig. 2, from a model of the cloaca and ducts. The length of the duct which will disappear in the first stage of the change is very evident, but there are no such definite indications of the extent of the duct, proximal to the ureter, which will be taken up in completing the second stage.

THE SUBCLOACAL MESODERMS

In fig. 2 the various stages figured are represented with indications of mesodermal beds in relation with their walls. Since these mesodermal layers fix the lower part of the cloaca and bear settled relations to the Wolffian duct,

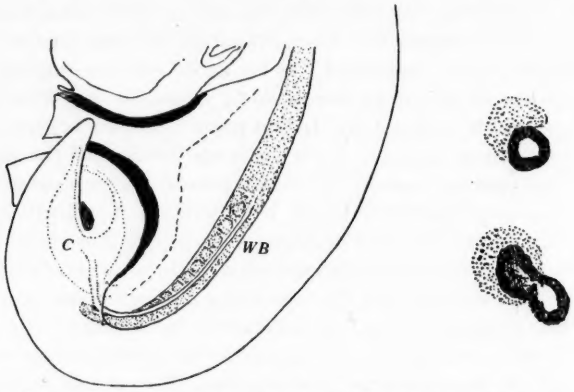

Fig. 1. Wolffian body (*WB*) and duct projected on to outline of embryo of 4·9 mm. Showing the duct crossing obliquely ventral to the Wolffian body. *C*, cloaca. The smaller figures are from sections across the duct where it lies ventral to *WB*, from embryos of 4·9 and 5 mm., as in text.

and are to be considered in construing the observations made on its changes, they will be dealt with shortly here: it will be seen also that they provide the basis and regional extensions for the growth and changes in the lower parts of the cloaca.

For present purposes the various mesoderms concerned can be illustrated sufficiently by the drawings in fig. 2. The first of these is from an embryo of less than 5 mm. length. In this the cloacal plate, *CP*, extends just on to the base of the body stalk, and there is thus no area of the body wall at all which could be called infra-umbilical. A very active mitosis is going on here among the cells immediately adjacent to this anterior end of the membrane, within the base of the body stalk, and this mitotic activity extends caudally from here on both sides of the plate, under the ectoderm. Its position is marked in the drawings by the dotted areas.

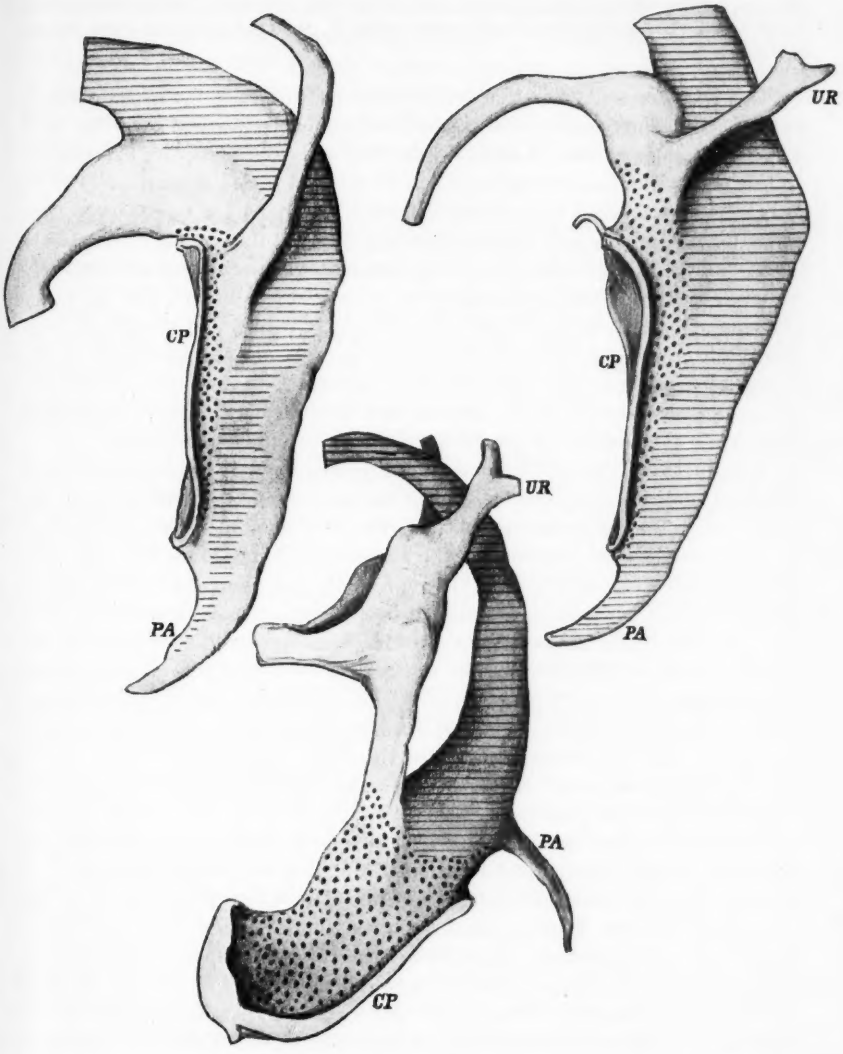

Fig. 2. Form of lining walls of the cavities from specimens of 4·9, 5, and 8 mm. length. ×100. Marked to show mesodermal relations, as described in text. *CP*, cloacal plate; *PA*, post-anal gut; *UR*, ureter. From models.

It is to be understood that the models represent only the lining cellular walls of the cavities, so that the mesodermal areas marked on them only show the positions of the layers where they are in contact with these walls. They do not show the whole extent of the layers.

This mesodermal bed, in this young specimen, cannot be followed definitely to the level of the caudal end of the membrane, but in the next drawing, from a specimen slightly older, 5 mm., it now surrounds this structure completely. In this paper the mesodermal layer can be referred to as "central".

The region marked by horizontal lines is covered by a mesodermal condensation continuous with that surrounding the gut tube: it may conveniently be referred to as "splanchnic". In the first embryo the layer is not definitely recognisable throughout, and only seems to extend in a broken way on to the post-anal gut, but in the 5 mm. specimen it is complete throughout. This splanchnic mesoderm seems to be the active agent in the formation of the cloacal septum, and builds in its growth a very thick condensation between its enclosed tube and that of the ventral part of the cloaca. The Wolffian duct reaches the cloaca in the angle between these two mesodermal beds.

The duct and the cranial part of the cloaca are left unmarked in these drawings, indicating that they are not covered or enclosed by either of the two mesoderms already mentioned. The mesoderm covering the cloacal portion, continuous with that surrounding the allantoic prolongation within the cord, is a loose non-condensed layer. Although easily distinguished in these earlier stages from the central condensation, it is of course continuous with it in position, and the central bed can be looked on from this point of view as a condensation particularly affecting the ventral portion of the general mesodermal surroundings of this part of the cloaca. Later, the distinction between the two subdivisions of this mesodermal bed becomes less marked, and there is reason to suppose that the contiguous part of the central thickening is "paid into" the other as the contained cavity elongates, thus affording a loose covering for it and permitting its growth.

The Wolffian duct is surrounded by a mesoderm which becomes continuous with the "cloacal" layer just mentioned, but it is not clearly assignable, at first at any rate, to a particular stratum. It must be remembered in this connection that the Wolffian duct is only a single cellular layer enclosing a lumen, not carrying round it any mesodermal sheath properly and peculiarly belonging to it: if it becomes functional it appears to get its mesodermal coat secondarily and locally. Towards the latter part of the changes we are considering, a definite thickening derived from that of the Wolffian body can be found especially along the concave surface of the duct, but this does not necessarily throw light on the earlier mesodermal value. Fortunately it is not a matter of importance from our present standpoint: it is enough for our purpose to recognise the presence of a more or less loose covering for all this region, including the part passing into the angle between the central and splanchnic strata.

The lower drawing in fig. 2 is from a specimen of 8 mm. It shows how the urogenital sinus is fixed in solid mesodermal condensations at its lower end, leaving the upper part free to expand, thus giving us a fixed region from which we can consider the effect of such expansion and growth, as will be seen later. It must be understood that the interval between the sinus and the rectum is filled, as far up as the peritoneal reflection, by thick splanchnic mesoderm, against which the sinus lies, although these things of course are not seen on the model.

It may be noticed here, incidentally, that the central mesoderm is concerned only, at first, with the making of anterior and lateral walls to the region of the cloacal membrane, and with the swinging round of this region, in a sagittal plane, so that it comes to face in an opposite direction. Growing at the base of the body stalk, and pushing back from this, it forms a genital tubercle at the front end of the membrane which not only separates this from the stalk, but, as it grows, carries this end of the membrane in a ventral direction. If we realise that, in the younger members of the embryos shown in fig. 2, the cloacal membrane faces actually cranio-dorsally, whereas in the 8 mm. specimen it is already looking ventro-caudally, we can appreciate the rapid change which has been brought about by the downward and caudal swing produced by the anterior growth, aided by the movement of the caudal end in the other direction in association with the atrophy and relative want of growth in this part. Up to this time the central growth adds practically nothing to infra-umbilical depth of belly wall, but is only concerned in reversing the "perineal plane" of the membrane and in building up the external genitals. This is of course combined with great increase in depth of the mesodermal bed surrounding the lower end of the urogenital sinus, with the addition of a new part to its channel—in fact, the lower half or so of the sinus is a new formation not derived from the original cloaca, but built up as an addition enclosed by the great mesodermal formations projecting beyond the *original* plane of the membrane. As soon as the "perineal plane" has been practically attained, we find the infra-umbilical central line slowly coming into being, continuous below with the genitalia, while the ventro-lateral formations of the body wall are beginning to find their way into contact with it.

The upper part of the cloaca, then, can be considered from an early stage as fixed below, itself covered only by a light mesodermal layer, which is no hindrance to its growth and expansion. This increase in its size is already apparent, dorso-laterally, in the 5 mm. specimen (fig. 2), and shortly after this its freedom is rendered greater by the extension of the coelomic angle between it and the rectum.

Some stages of this expansion, destined to form the bladder, are given in fig. 3. It can be seen in these that the widening proceeds outwards from the bladder towards the ureter, and is apparently purely a cloacal growth in the course of which the neighbouring portion of the Wolffian duct is lost. The expansion reaches the ureteric point at, or just before, the 12–12·5 mm. stage: the 12·5 mm. stage figured appears to indicate very well the terminal phenomenon of this first stage of the change.

It is necessary now to enquire into the disappearance of the Wolffian duct, with a view to seeing if possible how it is effected. Fortunately the 12·5 mm. specimen affords what seems to be a very satisfactory explanation of the process.

A series of sections of this embryo, passing through the parts concerned, are given in fig. 4: they form practically a continuous series, beginning at the ureteric point and working towards the main cavity.

These sections may almost be said to speak for themselves. The cellular duct wall, which has taken a deeper stain than the cellular layer lining the main

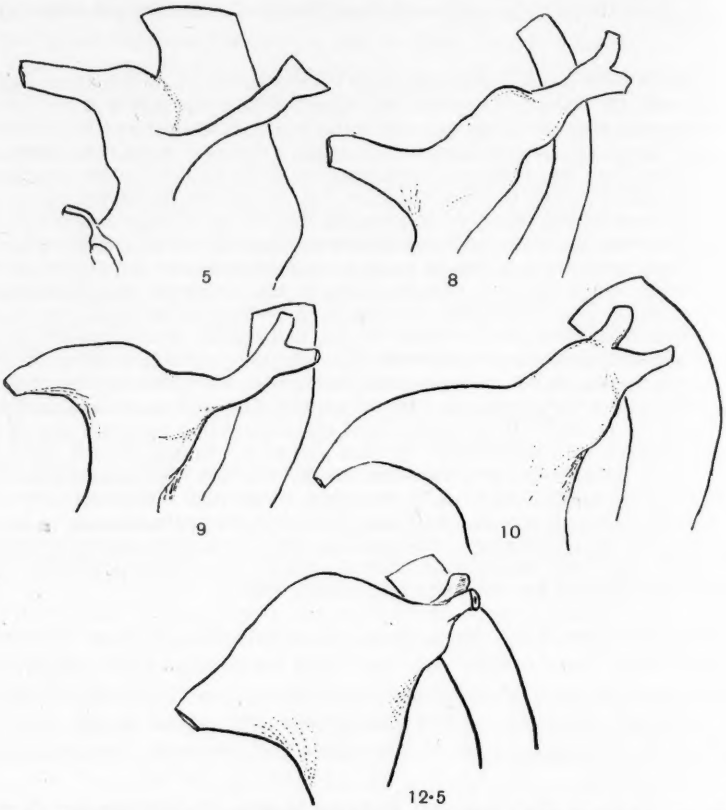

Fig. 3. To show the extension of cloacal expansion outwards along the Wolffian duct. Seen from left side: length in mm. recorded on each specimen.

cavity, is plainly seen to be carried on, into this latter region, half embedded in its lining layer, and showing no indication of any present or past enlargement. Cells of the main lining are to be found here and there on its superficial aspect, sometimes complete here but more usually fragmented, and in keeping with this we find the tendency for the superficial wall of the embedded duct to break up also, leaving the deep wall in position among the main cells.

There are certain points in these sections which will be mentioned later,

but it can be said at once that study of their appearances, and of other examples, led to formulation of an explanation of the constructions seen, which in its turn was easily put into a diagram. This is shown in fig. 5. The first drawing, A,

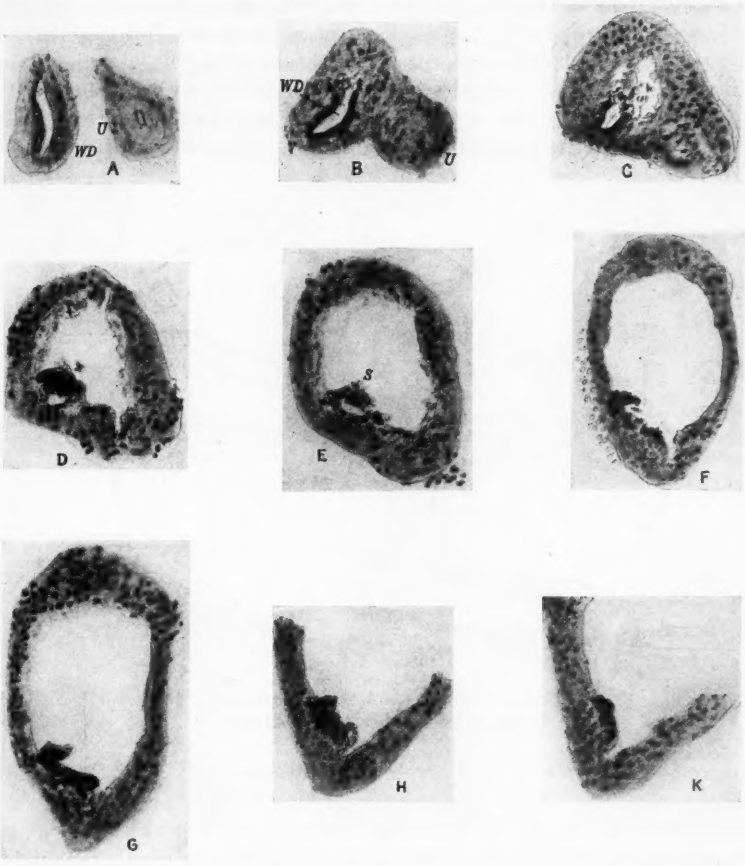

Fig. 4. A series of sections along the lateral projection of the sinus, beginning at the Wolffian duct (*WD*) and ureter (*U*), from an embryo of 12·5 mm. The series is complete except for two omitted just before the last. After K no sign of the duct remnant could be found. The lining cells of the sinus envelop the duct and ureter closely in A and B, and irregular degenerating remnants can be found along the duct, as in E at *S*.

shows the main lining layer, dotted, meeting that of the duct, lined. In B the main wall is folding itself over the duct, the dotted lines indicating the method of enlargement of the cavity. This leads to the condition in C, while D shows how the disappearance of this intussuscepted part leaves the duct opening in

its new position. C really embodies the principle of the process, which is a simple one, to be conceived as easily taking place if we remember that it concerns lining cells only, and not the surrounding mesodermal covering.

The lining cells folded in in this way do not appear to last very long, and I am inclined to think that the 12·5 mm. conditions are examples of a fortunate state in which their vitality was a little greater than usual. This view depends upon the seemingly rapid disappearance of the included cells in earlier stages, the shortness and broken condition of the remnants in another embryo of the same age, and the fact that in three embryos of 13 and 13·5 mm. there are no definite signs of the remnants to be found at all. All the stages before 12 mm.

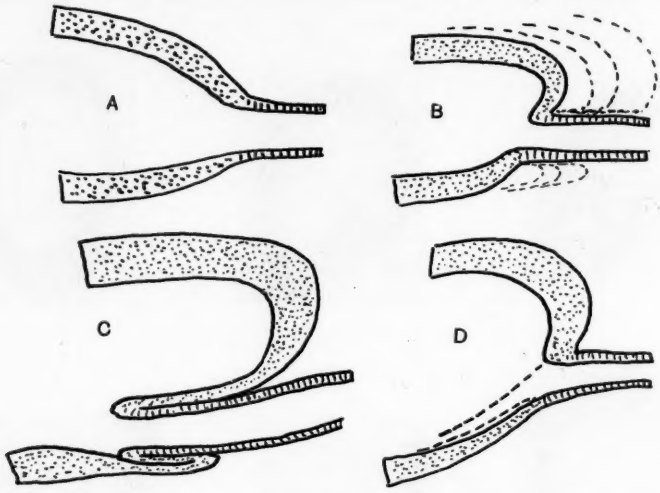

Fig. 5. Diagrams to show how the end of the Wolffian duct is "taken up" into the advancing cavity of the bladder.

show cellular remnants in this part, but in most cases these are short and near the advancing edge of the dilatation, suggesting that the parts found earlier have broken up. The 8 mm. specimen, however, has a practically complete inclusion which seems to represent—from its extent—the whole invagination so far as it has gone. It is given in the sections in fig. 6. The included cells show more of a delicate tracery than anything else, being presumably on the point of disappearing, but they have been beautifully fixed and preserved, and seem worthy of reproduction. It may be mentioned that the 10 mm. specimen was cut so obliquely that its cellular remnants were not suitable for reproduction, but this very obliquity gave one section which showed well the invaginated continuity between the duct wall and that of the growing bladder.

We may sum up the implications of the foregoing statements by saying that the first stage of disappearance of the duct is accomplished as a result of its

forming an intussusceptum within the growing bladder. The bladder cavity extends in this region clearly at the expense of the duct, not by opening it up but by destroying it, and the process of destruction involves not only the wall of the duct but also an inturned portion of the lining wall of the bladder. The bladder wall is the active agent, the duct being apparently passive.

The expansion of the bladder seemingly includes the terminal bit of the ureter in its spread, as may be seen in the sections in fig. 4. Thus the ureter gains

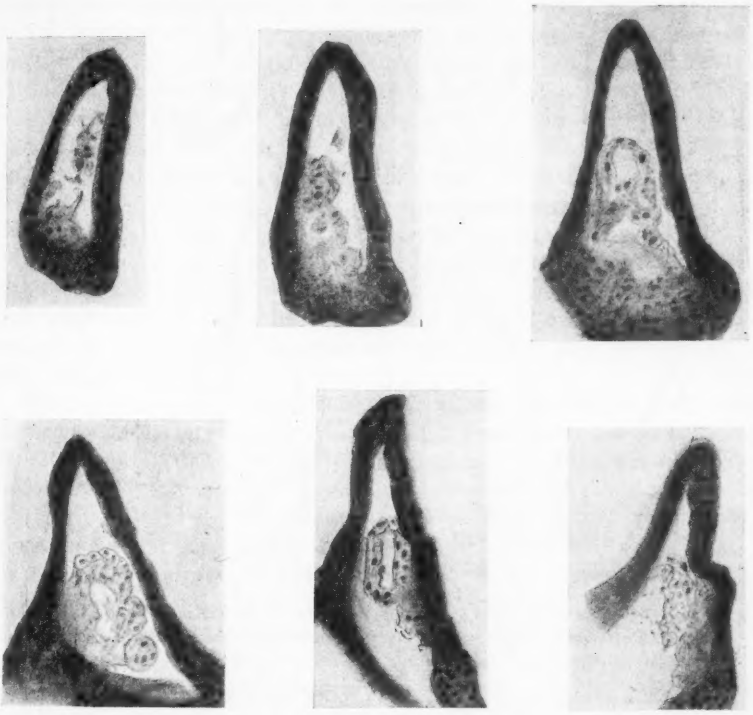

Fig. 6. A series of sections from the lateral dilatation of the sinus in an embryo of 8 mm. Sections pass towards the duct.

a separate opening into the bladder as a result of the same growth which has destroyed the duct, and there is no question of any duct value to be given to the intramural part of the ureter. The end of the bladder expansion thus leaves the ureteric and duct openings separated by a definite interval, the last mentioned being on the medial side: we need not consider here the slight change, probably purely mechanical, from the original position of the ureteric bud. The implanted ends of the two structures are surrounded by a thick mass of cells of

the lining layer, which may perhaps contain remnants of the included walls (but this is very uncertain), and it is from this arrangement of the structures that the second stage starts.

THE SECOND STAGE

The second stage of the change begins slowly and gathers speed as it progresses. There is little difference in level of the end of the duct between 13 and 15 mm., but 16, 17, and 18 mm. show increasing amounts of difference.

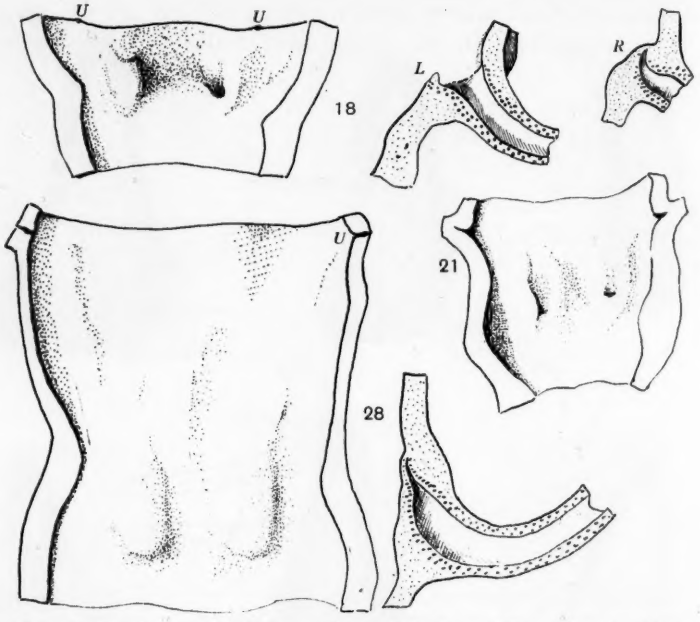

Fig. 7. Dorsal walls of urogenital sinuses, embryos of 18, 21, and 28 mm. length. Also sections along lines of Wolffian ducts showing their positions in the sinus walls. L=left; R=right; U=ureter.

Three degrees in this stage are shown in fig. 7, the last of which is from an embryo in which the Müllerian ducts are on the point of joining the urogenital sinus. The figures show the dorsal walls of the sinuses, with the impressions produced on them by the ducts, but linear reconstructions of sections along the lines of the ducts are also given with the corresponding surface views in two of the specimens: in the middle one the section was very much as in the first.

In the 18 mm. example the left duct opens on the surface, but the right one is blocked by a mass of cells, continuous above with rough epithelial debris which can be followed up to the remnant of the epithelial mass already mentioned as occupying the ureteral angle of the bladder. The sections show that the ends of the ducts are turned up and embedded in the lining cells of the cavity,

which have not given way to permit an opening on the right side. In the 21 mm. specimen the conditions are somewhat similar, except that both ducts are open here and the track of the right one is seen as a shallow groove on the surface: the distance from the ureter is slightly greater, and epithelial debris is still to be found. In the 28 mm. embryo, however, the distance from the ureters has increased to a very great extent, while the upturned ends of the ducts among the lining cells of the sinus are not open, but are covered by cells belonging partly to themselves and partly to the sinus: there is no epithelial track connecting them with the ureteric region.

The meaning of these observations seems reasonably clear up to a point. Mention was made, when dealing with the mesodermal strata, of a condensation continuous with the Wolffian mesoderm which appeared in association with the duct: this layer has formed before the end of the first stage, and is placed on the upper surface of the duct. Whether due to this or not is hard to say, but the duct appears to be held in position in a mass of mesoderm just behind the sinus, of which mass the condensation just spoken of forms the superficial part. The mesodermal mass has gradually become more pronounced during the progress of the first stage, forming a curved shelf in front of, and ventro-lateral to the peritoneal recess separating it from the rectum. It is continuous centrally with what is left of the older layer in the "angle", and may be taken to represent it. It forms the beginning and lowest part of the "genital cord" of a later stage.

Fixed, then, in this mesodermal condensation, the Wolffian duct passes forward to the dorsal wall of the sinus, which it reaches medial to the ureter. Here it is continued into the clump of lining cells, already spoken of as filling this part, and is lost among these. It must be remembered that we are dealing with a tube made by a single layer of cells, not carrying any special wall of mesoderm around them, and that the vesical end of this tube is embedded in the lining cells of the growing bladder: both these lining layers, therefore, are within and are enclosed by the common mesodermal covering of the bladder. Thus, as the vesical structures elongate in a direction away from the fixed lower part of the sinus, the implanted end of the duct is drawn up, making a curve with the fixed part: this upturned end is still enclosed by the common mesodermal coat, and embedded in the thick lining layer of the main cavity. Thus, as the growth goes on, the embedded part is found at relatively lower and lower levels, compared with the ureter, since it is fixed by the fixation of the duct, while the ureteric levels are carried away from it. The superficial wall of the embedded part, breaking down and disappearing in a way reminiscent of the first stage, leaves the final opening at the lowest level. The general idea of the way in which the level of the final opening is attained is embodied in the first scheme in fig. 8.

Although this general idea, diagrammatically shown, is without doubt correct, many details of the process are and must be uncertain. The rapid growth in length of the main sinus, especially in the latter part of the second

month, is associated with the rapid growth of the infra-umbilical belly wall, and its fixation below makes the extension effective in an upward direction.

A point at issue concerns the values of the area between the ureters and the openings of the ducts in the prostatic urethra, particularly the lines within that area extending down from the one-time openings of the ducts, medial to, and a little below the ureters, to the prostatic openings. It might be put into the form of a question—Does such a line contain along its length remains of the cellular wall of a duct, or are such remnants to be expected only in its lower part? It may be said at once that careful examination of the wall has failed to reveal anything suggesting cellular remains from the duct, except in the positions indicated in fig. 7, but this negative result does not allow one to

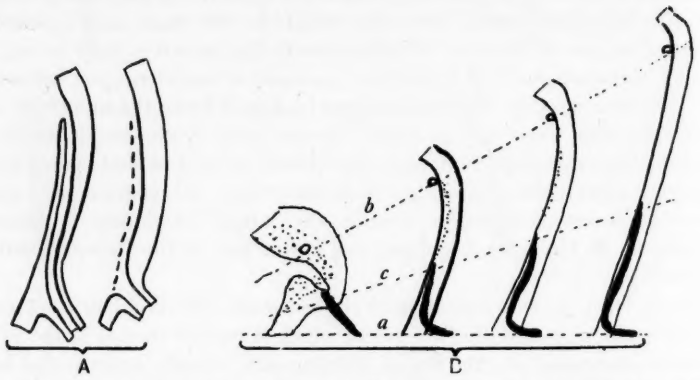

Fig. 8. These diagrams represent only the lining cell layers. A. To show the method by which the actual opening of the duct is gained. The superficial wall of the embedded part breaks down and disappears (interrupted line in second figure), leaving orifice of duct at its low level. B. Diagrams to show the effect on duct (black) and ureteric level of growth of sinus upwards from the fixed level (*a*). The ureteric orifice is raised most (*b*), while the embedded end of the duct is not only turned up but also lengthened (*c*) to a smaller extent. The epithelial mass (dotted) round openings of ureter and duct in the first figure is hollowed to a small funnel and then drawn out between *b* and *c*.

assume that such "remains" may not be there, indistinguishable among the cells of the lining layer. Such, in fact, was the way in which I was inclined at first to look at these results, but it was not only an unsatisfactory standpoint in itself, but did not agree with certain minor matters of observation: hence this view of the conditions was given up.

If it is remembered that the level of the duct, behind the sinus, is fixed by surrounding mesoderm, and that in consequence any increase in length of the main cavity, in keeping with infra-umbilical extension, must be an increase only in an upward direction, the nature of the changes becomes clearer. Moreover, it becomes apparent that the ultimate opening is only an expression of the fixed lower level, that it is not in fact an indication of any downward

shifting of the orifice of the duct, but of a growth of the ureteric and other levels upwards away from it.

The effect on the end of the duct of the beginning of this upward extension is of interest. It was pointed out above that a thick collection of cells occupies the "angle" of the main cavity into which the duct and ureter are inserted at the end of the first stage: it seems to be associated mostly with the end of the duct. The effect of the upgrowth is at once apparent in an upturning of the vesical end of the duct and, connected with this, a decided appearance of drawing downward and backward of the thick cellular collection—in fact, there is a short funnel-shaped recess of the cavity, lined by thickened cell layers, passing backwards and downwards and receiving the end of the duct. Thus, apparently by some stretching of this cellular mass, a small but distinct difference between the duct level and that of the ureter becomes evident at once.

It is possible that this recess formation is in some way a prolongation or extension of the process described in the first stage, now involving the duct only, and complicated by the beginning of upgrowth. The appearance of cell arrangement in some of the sections examined suggested this possibility, but it could not be established certainly. If it were so it would make first and second stages an entirely continuous movement, with somewhat different appearances resulting from it.

This difference of level being established, growth of the walls goes on with increasing rapidity, one of the earlier results being the opening out of the short "recess", so that its thickened lining is now spread between the ureter and the end of the duct. This seems the most likely explanation of the rather rapid disappearance of the recess, and accounts at the same time for the presence of the epithelial debris and thickened patches found (fig. 7) between the ureter and the end of the duct.

The terminal piece of the duct is turned up as a result of the upward growth, and is lying within the mesodermal coat enclosing the sinus, so that, as the recess flattens out, the upturned duct wall blends with the cells lining the sinus. Thus we get the conditions seen in fig. 7. Then, as growth goes on, the lower parts of the wall do not extend so far as the upper part; but there is some extension of it nevertheless, and the upturned end of the duct is elongated accordingly. Thus we find some explanation of its increasing length in the specimens in fig. 7. An attempt to express schematically this view of the mode of growth is given in fig. 8 B.

This conception of the processes of change through which the region passes, in the second stage, avoids the necessity for assuming the presence of duct remnants in the upper part of the line, accounts for the actual lengthening which takes place in the upturned end of the duct, and has the ultimate level of its opening fixed from the beginning, it being necessary only for the covering anterior wall of the embedded portion to degenerate in order that the final orifice may be discovered at its proper level. The remnant line, reaching well into the bladder, is that in which an accessory ureter will open. It is possible

that an additional ureteric opening close to the normal one might come from an immediate division of the primary bud, being taken into the bladder by that overlapping of the ureter, by the sinus lining, which we have seen to occur in the 12·5 mm. specimen: lower down, however, the embedded end of the duct would be responsible for it as a separate outgrowth.

In this second stage, although the embedded and upturned part of the duct shows a relatively fair length, this is only a secondary character, and the actual piece of the duct concerned, if put in terms of the early and complete duct, would probably be exceedingly short.

SUMMARY

The paper deals with two stages in the disappearance of the end of the Wolffian duct: firstly where the part beyond the metanephric bud disappears in the bladder, and secondly where its opening comes to lie in the prostatic region.

A brief account of subcloacal mesodermal beds is given, to show how the cloaca is fixed below, leaving its upper urogenital part free to expand.

The first stage is effected by extension of the sinus along the duct, up to and just including the ureteric origin, the enclosed duct forming an intussusceptum (with the infolded sinus lining) which rapidly degenerates and disappears.

The second stage, following immediately, is marked by fixation of the duct by mesodermal condensation behind the sinus, with growth of this latter upwards in keeping with the growth of the infra-umbilical belly wall. The implanted end of the duct is thus turned up within the lining layer of the sinus, always at its lowest part, and the breaking down and disappearance of its front wall discovers the opening at the lowest level. In the meantime the upgrowth of the main cavity carries the ureteric levels farther and farther away.

The upturned end of the duct, originally short, is lengthened to some extent in the general lengthening of the wall, thus reaching well into the bladder. This provides a duct "remnant line" in which any structures (such as an accessory ureter) connected with the duct will be placed.

THE ANATOMY OF THE MAJOR DUODENAL PAPILLA OF MAN, WITH SPECIAL REFERENCE TO ITS MUSCULATURE[1]

By VINCENT J. DARDINSKI, M.D.[2]
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The major duodenal papilla is that portion of the duodenum through which, in the majority of instances, the common bile duct and the main pancreatic duct, or duct of Wirsung, empty their respective secretions into the intestine. Under normal conditions it is situated on the medial aspect of the descending portion of the duodenum, approximately 7·5 cm. from the pyloric valve of the stomach. It is not to be confused with the minor duodenal papilla through which the accessory pancreatic duct, or duct of Santorini, sometimes empties into the duodenum. The latter is found in the same portion of the duodenum as the former, but it is usually 2–3 cm. nearer to the pyloric valve and is much smaller.

The appreciation of the importance of the major duodenal papilla and the part it may play in regulating the flow of bile dates back to Glisson (5) in 1681. He was the first to suspect a sphincter muscle in this region but gave no proof of its presence.

In 1685 Govert Bidloo (2) first noted the major papilla as being a common outlet for both the bile and pancreatic ducts. In 1879 Gage (3), an American zoologist, gave the first anatomic description of this region in the cat. In his work he stated: "The terminal portion of the common duct in the cat, as it passes obliquely through the intestinal muscular layers, is surrounded by a narrow layer of smooth muscle fibres. A similar layer is found around the terminal part of the pancreatic duct. These fibres are sphincter fibres and appear to be intimately connected with the fibres of the intestinal musculature, making it difficult to separate one from the other." He added further, "there is another sphincter common to both ducts formed by the intestinal musculature".

Oddi and Marcacci (14), while studying the effects of cholecystectomy on animals in 1887, noticed dilatation of all the extrahepatic ducts, especially the cystic duct. They were of the opinion that this was a compensation for the absence of a gall bladder. From this observation Oddi concluded that in order to produce this effect a sphincter must be present at the termination of the common duct. He thereupon set out to prove this by investigating the region in various animals, such as the dog, rabbit, ox, hog, cat, and horse. In all of

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these animals he found a similar disposition of muscle fibres in the region where the common duct penetrates the intestinal musculature, and he stated that these fibres constituted the sphincter of the common duct. He also described a similar muscular disposition around the terminal portion of the pancreatic duct and a common sphincter for both ducts formed by the intestinal musculature. The individual sphincter muscles of the ducts, he stated, are independent of the intestinal muscle.

Hendrickson (7), in 1898, described the musculature of the extra-hepatic biliary system of the dog, rabbit, and man. He concluded that in all of these a sphincter muscle was present. Helly (6), Letulle and Nattan-Larrier (10), Matzuno (13), Job (8), Mann (11,12) and his collaborators (4,9), and others have contributed to this subject, and the conclusions reached by them are confirmatory of the work done by the foregoing investigators, that is, that an independent sphincter muscle is present at the intramural portion of the common duct. In 1922, Auster and Crohn (1) stated definitely that they found no structure in this region that they could call a sphincter or any structure that resembled other sphincters in the body.

A complete anatomic and histologic study of this region was made on twenty-one specimens obtained at necropsy by Letulle and Nattan-Larrier. Most of their conclusions, however, were based on microscopic study of sections.

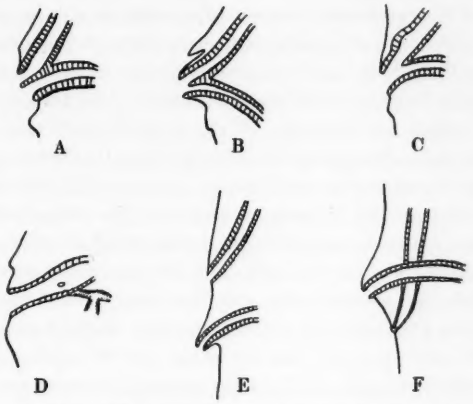
Because of the complicated picture presented by a histologic section of this region and the infrequency of a complete study of the papilla and its relation to the surrounding intestinal muscle, it was deemed advisable to carry on a more complete investigation.

The work that I wish to present is the result of my study at necropsy of duodenal papillae and associated ducts in 100 cases. Microscopic dissection was made of thirty different specimens after treatment for several days in Marcacci's macerating fluid, which consists of equal parts of concentrated nitric acid, glycerine, and water. Macroscopic examination was made to determine the point of termination of the common and pancreatic ducts and the frequency of true ampullar dilatation within the papilla.

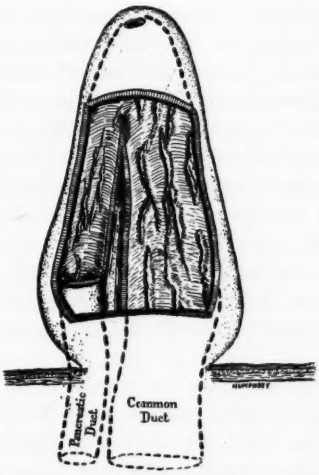
The results obtained with regard to the presence of an ampulla and the point of termination of the ducts are as follows: In fifty-one cases both ducts emptied separately into the tip of the papilla. In twelve cases both ducts united in the papilla 1 mm. from its outlet, in five cases 2 mm. from its outlet, in twelve 3 mm. from its outlet, in ten 4 mm. from its outlet, in four 5 mm. from its outlet, and in four 1 cm. from its outlet. In one case both ducts emptied separately into the intestine, and in one case the pancreatic duct passed through the major papilla, and the common duct passed through a slit-like opening in the wall of the intestine 1 cm. below the tip of the papilla (text-fig. 1).

True ampullar dilatation within the papilla is present in those cases in which the two ducts unite 5 mm. or more from the outlet. In the remainder both ducts are separated by a thin membrane, formed by the adjacent walls of the pancreatic and the common ducts, which extends from the base of the

papilla to the point where they unite. In fifty-one cases or 51 per cent., however, this membranous partition extended from the base of the papilla to the



Text-fig. 1. Points of termination of common bile and pancreatic ducts in 100 cases at necropsy were as follows: as in A in fifty-one cases, as in B and C in forty-three cases, as in D in four cases, as in E in one case, and as in F in one case.



Text-fig. 2. The course of the common and pancreatic ducts within the papilla. A window has been cut out to show the membranous partition separating the two ducts. As can be seen, this membrane is formed by the adjacent walls of the two ducts and extends toward the tip of the papilla where the two ducts unite to form the ampulla.

outlet, so that the two ducts did not unite and no ampulla was formed (text-figs. 1 and 2).

The mucosa within the ampulla has been mentioned by Matzuno, Helly, Opie, Letulle and Nattan-Larrier, and Mann (11) as being thrown into numerous longitudinal folds, but none of these has given any description of it. Mann and Letulle and Nattan-Larrier refer to the folds as valves, and mention the fact that these valves are often seen projecting through the outlet of the papilla.

By studying Plate I, fig. 1, the following observations can readily be made: There is an abrupt change of the inner structure of the terminal portion of the common duct, which for purposes of description is divided into the extraduodenal and intraduodenal portions. The dividing line between these portions can readily be seen and corresponds to the point at which the intestinal muscle surrounds the duct, or the intramural portion. The extraduodenal portion is fairly smooth and contains numerous large pits which are the outlets of sacculi found in the wall of the common duct. The intraduodenal portion is composed of numerous folds that course longitudinally; these folds vary from 2 to 4 mm. in length and from 2 to 3 mm. in width. On closer study it can be seen that the tip or end of one fold fuses with the tip or the side of another fold, forming by this union a pocket or cavity that in the majority of instances roughly corresponds to a triangle with its base directed toward the extraduodenal portion of the common duct. The triangular appearance, however, is not always apparent, for many appear elliptical in shape and others only as a slit-like opening. The size or depth of the pocket formed is not constant and each one is different from the next in some respect. It can be seen that these pockets are found around the entire inner surface of the papilla, and, as one passes toward the tip, the pockets are seen to become smaller and more shallow. In the final 1–2 mm. of the papilla these longitudinal folds do not fuse but hang free, their tips sometimes extending through the outlet of the papilla.

The intrapapillary portion of the pancreatic duct contains similar folds, but they are smaller in size and are not as prominent as those in the intrapapillary portion of the common duct and they do not arrange themselves to form such pockets as have already been described.

Such a complicated arrangement is not abnormal nor the result of inflammatory adhesions because it is present in various aged foetuses and persists throughout life. The youngest foetus that I have studied was five and a half months old.

The important point to be mentioned here is that the greatest point of constriction of the common duct is always present in the intramural area and always corresponds to the region where the intestinal muscle surrounds it. It does not correspond to the independent muscle fibres which will be described later.

The external surface of the papilla, with its relation to the surrounding intestinal musculature, together with the relation of the terminal portions of the common and pancreatic ducts, can best be described from actual dissection using a dissecting microscope, because what was found by actual dissection was later confirmed by study of serial sections.

The best results from actual dissection were obtained by placing fresh unembalmed or unpreserved specimens in Marcacci's macerating fluid for from 48 to 72 hours. At the end of this time dissections were made under water using fine instruments, such as those used in surgery of the eye.

The mucosa and submucosa of the duodenum covering the external surface of the papilla are removed without difficulty, and, if one is careful, it will be observed that the blood supply to the papilla is obtained from four main blood vessels (text-fig. 3*a*). Two of these blood vessels are situated on either side of the base, just at the point of penetration of the papilla through the intestinal musculature, and two are found on either side, at the tip of the papilla. These vessels are small and give off numerous branches. Some of the branches come off the main vessel immediately after it penetrates the intestinal musculature; others arise at irregular points from the main vessel as it passes along the side of the papilla. All four main vessels, however, continue along the side of the papilla, and their numerous branches supply the papilla and the surrounding intestinal musculature.

The nerve supply of the papilla can also be seen at this stage, for at the point where the four vessels penetrate the intestinal muscle there can be seen white, glistening fibres that more or less follow the course of the blood vessels and give off numerous branches. Many of these can be traced to the papilla where, in their course, at the point of branching, the fibres appear to be definitely swollen. These swellings of the nerve fibres correspond to the ganglia that Oddi (15) described in 1894.

The removal of the blood vessels, nerves, and submucosa leaves the muscle bundles of the inner, circular intestinal muscle stained light yellow. The papilla is now seen lying in a trough formed by the inner layer of intestinal muscle, and it is attached to the latter by connective tissue (text-fig. 3*b*). At the base of the papilla are the circular intestinal muscle bundles, some of which take a curved course as they pass over it (text-fig. 3*c*).

With the specimen held in place the papilla can be pulled forward. When this is done a few, narrow, flat, ribbon-like bands of muscle fibres will be seen which appear to be independent of the intestinal muscle at the base of the papilla. These fibres are only four or five in number, and are very loosely arranged (text-fig. 3*d*). Turning the papilla to one side, some of these fibres are seen running forward to become attached to the circular muscle of the intestine (text-fig. 3*d* and *e*). The remainder run obliquely forward and downward around the side of the papilla to the under surface where their ends either become invisible in the dense connective tissue or they interdigitate with the opposite end of the same or other fibres (text-fig. 3*b*).

This group of fibres at the base of the papilla, best seen in text-fig. 3*d* and *e*, are the only fibres that would correspond to Oddi's description of the sphincter muscle of the common duct.

If the circular muscle of the intestine is now removed from the base of the papilla, a groove is readily seen encircling the common duct just posterior to

the narrow layer of fibres, which was described above (text-fig. 3*e*). This groove is formed by the circular muscle of the intestine and corresponds to the most constricted portion of the duct on the inside. Now also can be seen the longitudinal muscle of the intestine, whose fibres are small and loosely arranged around the common duct (text-fig. 3*d*). Some of these fibres are found running forward on the under surface of the papilla and become lost in the dense connective tissue (text-fig. 3*b*). Others swing laterally away from their normal course and blend with the circular muscle of the intestine (text-fig. 3*d*).

Separating the fibres of the layer of longitudinal intestinal muscle and cutting the attachment of the few fibres extending from the base of the papilla to the circular intestinal muscle, the entire papilla can be removed without difficulty. The pancreatic duct is now seen on the ventral surface of the common duct (text-fig. 3*b*). It passes forward in this position next to the common duct, and the groove described around the common duct, formed by the circular intestinal muscle, is also found around the pancreatic duct, just before it comes to lie in apposition to the common duct. Both ducts are now seen running forward through the papilla and are enclosed by dense connective tissue and loosely arranged muscle fibres which are next to be described (text-fig. 2).

Dissection of the removed papilla can easily be made by pinning it down. The mucosa and submucosa having already been removed, its surface is found covered with dense connective tissue. By careful dissection and removal of this connective tissue, very small, white nodules, 1–2 mm. in diameter, can be seen scattered over the surface of the papilla. These are found to be attached to the papilla by a short narrow neck which is surrounded by smooth muscle fibres (text-fig. 3*c*). On section these nodules are found to be racemose mucous glands (Plate I, fig. 2), and they empty into the lumen of the papilla

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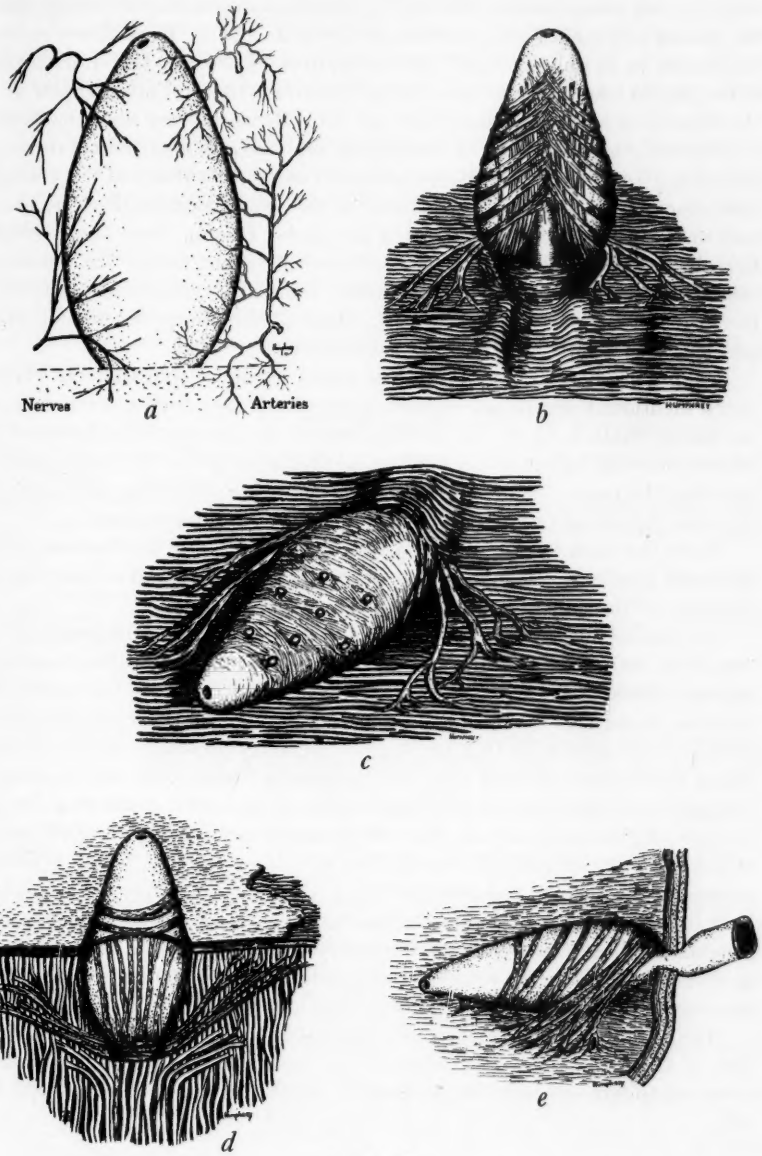
Explanation of text-fig 3.

Text-fig. 3. *a*, the nerve and blood supply of the papilla. Since the same arrangement is found on both sides, one figure is used to indicate the nerve supply on one side and the blood supply on the other. The small swellings at the point of branching of the nerves represent the ganglia that were first mentioned by Oddi. *b*, the papilla elevated from the trough formed by the duodenal wall showing the arrangement of fibres on the under surface. In the centre of the lower portion of the papilla can be seen the pancreatic duct which gradually becomes invisible as it passes toward the tip of the papilla. *c*, the papilla and part of the duodenal wall from which the mucosa and submucosa have been removed. The surface of the papilla is covered with numerous white nodules which are the racemose mucous glands. These empty into the lumen of the papilla by way of a short neck. Around the necks of these glands can be seen the muscle fibres of the papilla, which by their arrangement no doubt have some effect on the outflow of secretion from these glands. *d*, the papilla lying on the duodenal wall. The mucosa, submucosa, and most of the obliquely coursing fibres have been removed from the papilla to show the deeper-lying longitudinal fibres. At the base of the papilla is the bundle of fibres which would correspond to the sphincter of Oddi. The mucosa, submucosa, and the inner circular muscle of the intestine have been removed to show the arrangement of the longitudinal muscle fibres of the intestine. *e*, the common duct as it passes through the central wall. The constriction of the duct can readily be seen. The mucosa and submucosa have been removed from the papilla to show the arrangement of the obliquely coursing fibres.



Text-fig. 3.

by way of the neck. Further dissection through the thick layer of connective tissue reveals many narrow, thin, loosely arranged muscle fibres through which the glands just mentioned penetrate (text-fig. 3*c* and *e*). These fibres encircle the papilla in an oblique course, extending over the sides to the under surface of the papilla where they become lost in connective tissue or interdigitate as do the fibres previously described (text-fig. 3*b*). Beneath these fibres and intermixing with them are fibres of similar size that run in a longitudinal direction (text-fig. 3*b* and *d*); these extend backward along the surface of the common and pancreatic ducts and become lost in the dense connective tissue of the wall in the extraduodenal portions of the ducts. Tracing these fibres forward toward the tip of the papilla they become invisible, under the dissecting microscope, at the points where the bases of the longitudinal mucous folds on the inside of the papilla are attached. Many of the obliquely coursing fibres previously described have a similar termination.

From a study of the serial sections made, it can be seen that the various fibres mentioned are found extending into the longitudinal mucous folds on the inside (Plate I, fig. 3). The sections reveal that the epithelial lining of the folds is of a tall columnar variety similar to that found in the common duct, also that the mucous glands previously mentioned on the surface of the papilla are more numerous around the terminal part of the common duct.

From the work here presented a logical explanation of the function of the duodenal papilla is suggested. It is entirely hypothetical and is based on the structure of the papilla and its muscular arrangement.

The flow of bile appears to be controlled by the tonicity of the inner circular muscle of the intestine. When, by peristalsis or nerve control, this tonicity is relaxed, the fibres extending from the base of the papilla to the wall of the intestine, as seen in text-fig. 3*c*, *d* and *e*, contract, and this contraction probably occurs at the same time that the tone of the inner circular muscle is relaxed. When these fibres contract they pull the papilla forward, thereby tending to straighten out the duct at the point where it had been constricted by the surrounding intestinal muscle. This action would naturally open up the lumen of the duct at this point of constriction and allow the bile, which is always present in the duct, to flow into the lumen of the papilla. Here the bile is held back in the pockets surrounding the lumen of the papilla and accumulates until the muscle fibres which surround the papilla contract. By this contraction the pockets on the inside are reduced to a minimum, and at the same time there is squeezing of the papilla that expels the bile in a spurt.

The effect on the pancreatic duct is probably the same, that is, the contraction of the fibres tends to straighten out the duct and allows the retained secretion to flow out into the papilla from which it is expelled mixed with the bile.

CONCLUSIONS

1. The greatest constriction of the common duct is produced by the intestinal muscle. This would seem to be the most logical point of the sphincteric action, if there is any, and would seem to be produced by the intestinal muscle.

2. The independent muscle fibres, described by Oddi as being responsible for sphincteric action, are not circular in their arrangement but oblique, and the point of greatest constriction of the common duct is not outlined by these fibres.

3. The longitudinal mucous folds within the papilla have a definite arrangement, and the presence of muscle fibres in these folds would indicate that they have an active part.

4. The mucous glands present are direct outgrowths of the epithelial lining of the papilla.

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EXPLANATION OF PLATE I

Fig. 1. The intrapapillary and extraduodenal portions of the common bile duct.

Fig. 2. Section through one of the white nodules found on the surface of the papilla, showing many alveoli. The cells are columnar and contain mucus (× 72).

Fig. 3. Section of the longitudinal mucous fold on the inside of the papilla, showing the presence of many smooth muscle fibres running in a longitudinal direction. The fibres in the photograph are stained black in contrast with the remainder of the section (× 96).

Fig. 1.

Fig. 2.

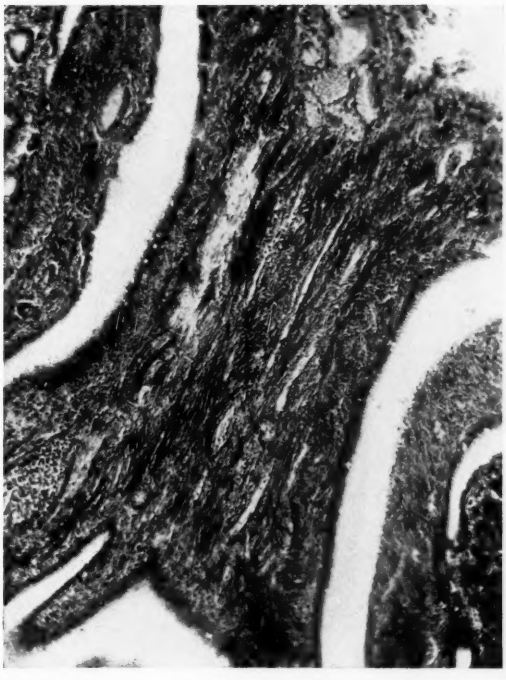

Fig. 3.

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PARAGANGLIA AND CAROTID BODY

By Prof. A. CELESTINO DA COSTA (*Lisbon*)

I had occasion seventeen years ago to study the development of the sympathetic nervous system of the bat in connection with researches on the origin and the formation of the adrenal glands. As is well known, the pars medullaris of these organs and the sympathetic ganglia take origin from the same matrix, the protosympathetic cord. I observed that in some Vespertilionidae (*Myotys*, *Vesperugo serotinus*, *V. abramus*, *V. pipistrellus* and *Miniopterus schreibersii*) two kinds of cells differentiate in the sympathetic cord which evolve in very different ways. One of these cellular varieties is composed of large cells, possessing large, oval, hypochromatic nuclei; the other comprises small elements mingled with fine fibres. The structure and evolution of the latter show that they represent the nervous ganglionic cells of the sympathetic system; they appear distinctly later in the embryo than the cerebro-rachidian ganglionic nerve cells. The cells of the spinal ganglia show already a nervous structure at a time when the sympathetic ganglionic elements are still in a backward state. In contrast with this slowness in differentiation of the sympathetic nerve cells are the large and well-developed paraganglionic cells that resemble closely the medullary cells of the adrenals, both formations being in contact at the lower part of the embryonic adrenal, where the medulla is continuous with the pre-aortic paraganglion.

During the later stages of development, the great masses of paraganglionic tissue that form enormous organs in the neck and in the abdomen regress. Their cells become smaller, and meanwhile the nervous sympathetic elements acquire the cytological structure of nerve cells. At a certain stage, both kinds of cells have more or less the same dimensions; later the ganglionic cells complete their differentiation and become much larger than the paraganglionic, but the medullary elements of the adrenal continue their development. As we know that the main function of this tissue consists in secreting adrenalin and that this product has the same physiological action as is obtained by exciting the sympathetic nervous system, we may interpret the particular evolution of both tissues, paraganglionic or chromaffin and sympathetic ganglionic, in the following way: during the first stages of embryonic life, the secretion of adrenalin supplies the function that is assumed later by the developing sympathetic. When this system is so differentiated that it can completely assume its function, most of the adrenalin-secreting tissue regresses, only persisting in the medulla of the adrenal and in some chromaffin bodies scattered through the organism. We can bring this possible substitution of a probable humoral mechanism by a predominant nervous mechanism into correlation with facts

of comparative anatomy already pointed out by J. F. Gaskell, namely the relative predominance of the chromaffin tissues over the sympathetic ganglia in Cyclostomes and Fishes, as compared with the inverse conditions in Mammals and other Vertebrates.

These peculiar features of the development of the sympathetic derivatives are nevertheless not constant in Mammals, for in the bats belonging to the family of the Rhinolophidae, the paraganglionic system never assumes a great morphological importance, whereas in those of the family Vespertilionidae it is much more developed. In other respects also, the Vespertilionidae and Rhinolophidae exhibit differences in their morphological characters.

I described some years ago the development of the paraganglionic tissue of the hedgehog, and I was able to show that in this Mammal there are great differences in the evolution of the paraganglionic cells that penetrate into the cortical primordium of the adrenal and those which remain mixed with the ganglionic elements. The former very soon assume their peculiar structure, the latter remain for a long time in a very rudimentary condition; the same can be said of the sympathetic nerve cells which also are very slow in differentiating. Moreover, in a personal communication, Prof. Goormaghtigh informs me that in the adult hedgehog the paraganglionic system is much developed, which means that the future extra-adrenal chromaffin cells develop much more slowly than the medullary cells.

This dissimilar behaviour of the components of the chromaffin tissue exists also in Man. Tokomitsu, Jachontoff, Hett, Kohno and others observed that, at the moment of birth, the suprarenal medulla exhibits a very rudimentary structure; the cells show little or no chromaffin reaction in contrast with the other paraganglia (Zuckerkandl's organ and others) that show a great development with well-marked chromaffin reaction. During the first stages of life these paraganglia regress and the suprarenal medulla assumes its peculiar structure and microchemical reactions.

All these facts lead to the conclusion that there exist considerable chronological differences following the species between the development of the sympathetic nerve cells, the paraganglionic adrenal cells and the paraganglionic extra-adrenal cells.

With the valuable aid of the Rockefeller Foundation, I have spent some months in the Department of Embryology of University College, London, studying the excellent and rich material of mammalian embryos, kindly placed at my disposal by Prof. J. P. Hill, to whom I express my gratitude.

In the rabbit, as in other species already studied, the development of the sympatheticus is remarkably late and slow. The prevertebral cord remains in an undifferentiated state up to the stage of 12 days (greatest length about 8 mm.) in which the first signs of a cellular differentiation are apparent. Meanwhile the cells of the spinal ganglia are already well differentiated and of indisputable nervous nature. The cellular differentiation of the sympathetic cord proceeds slowly but the conditions are very different in the cervical and

the trunk parts of the cord as compared with the abdominal pre-aortic plexus. In these regions, the embryos of 13 days show already two kinds of cells, the nervous situated in a medial position, the paraganglionic on the contrary in a lateral situation.

The cells that in embryos of 14 days are penetrating into the primordium of the cortical tissue differentiate more slowly. Only in the 15-day embryo can the development of these cells be compared with that of the pre-aortic plexus. The paraganglionic pre-aortic masses of the rabbit embryo assume a rather extensive development (Plate I, fig. 1, *P.G.*). In the medial part of these paraganglia, in close contact with the aorta, develop the ganglionic cells that differentiate very slowly. It must be noted that, mingled with these nerve cells, especially at some points, many rudimentary cells remain that constitute a third kind of embryonic sympathetic element, which persists in this condition up to advanced stages. The existence of these rudimentary cells has already been described by myself in the hedgehog. Here is the principal difference between rabbit or hedgehog and the Vespertilionidae in which nearly all the sympathetic embryonic cells are nervous or paraganglionic from the very first stages of the sympatheticus development.

The differences in comparison with the bats are still more considerable in the cervical region. The cervical sympathetic cord of the rabbit contains two kinds of cells, the future nerve cells that differentiate slowly and the rudimentary cells that remain in this condition up to advanced stages. The contrast with the large cervical paraganglia of the Vespertilionidae is very striking.

In the Marsupialia (*Trichosurus vulpecula*, *Phascolomys mitchelli*, *Dasyurus viverrinus*, *Didelphys aurita*) the paraganglionic tissue (Plate II, fig. 1) is not so developed as in the bats but more so than in the rabbit. The cytoplasm of the paraganglionic cells stains very intensively with haematoxylin, and these elements can be very easily detected in the embryonic sympathetic system. The cervical prevertebral cords are large formations in which the paraganglionic cells are very numerous, but not so great as in the bats. Small rudimentary cells are also to be observed in the sympathetic cords.

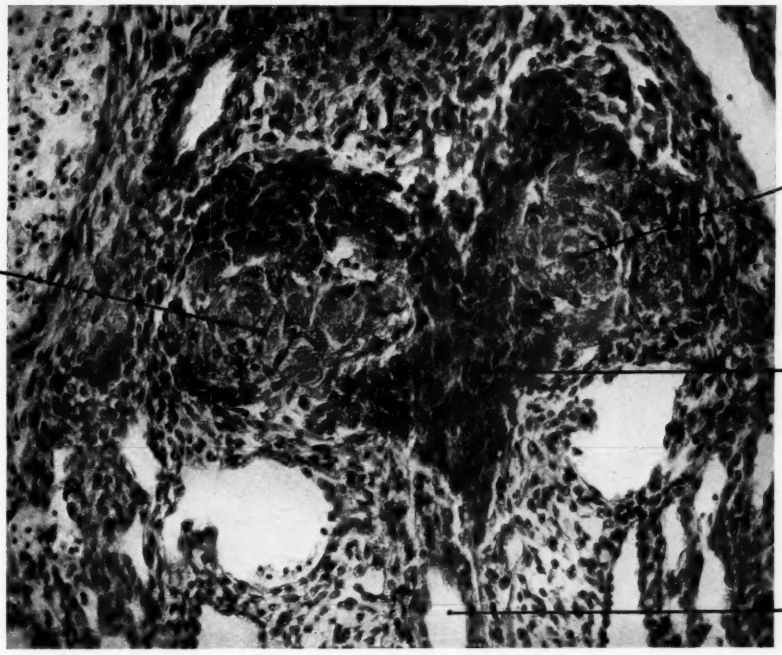
All these facts support the very fundamental notion that the sympathetic nervous system is a late acquisition of the body that differentiates and grows very slowly and that must begin to function undoubtedly later than the cerebrospinal nervous system. They show also that a great part of the elements that constitute the primordium of this system (in variable degree according to the species) can remain in a rudimentary state during a large part of embryonic life, possibly also for some time after birth, and that they have the possibility of differentiating much later. This can be noted in relation with the facts pointed out by Agduhr of a post-embryonic development of spinal neurones. It must also be kept in mind that three possibilities exist in the differentiation of the embryonic sympathetic elements: nervous cells, paraganglionic cells, Schwann's cells and their modalities.

One of the principal structures that is correlated with the development of

the sympathetic is the so-called carotid gland or carotid body. Many investigators have in recent years undertaken the study of this rather enigmatic structure. I do not intend to recapitulate here all that has been said upon this subject. Kohn's well-known theory of the chromaffin nature of these bodies has been denied by authors who were not able to obtain Henle's reaction, as de Castro did. Other views have been put forward. Hans Rabl described, in the guinea-pig, a mesodermic peri-carotid origin of the cells of the carotid body and suggested that these cells can become chromaffin. De Castro considers this organ as a sensory organ supplied with a centripetal innervation, mostly derived from the glosso-pharyngeus, and denies its glandular character. More recently Kohn and his pupils interpret the carotid body as a special kind of paraganglion, different from the other chromaffin adrenalin-producing bodies, but admit its origin from the sympathetic as did de Winiwarter. Muratori, in a study of the innervation of the glomus caroticus, points out the fact of the presence of paraganglionic cells in the ganglia of the vagus. He admits also two kinds of paraganglia, the sympathetic chromaffin bodies and the parasympathetic non-chromaffin bodies. The question is not yet settled and is still more complicated by the considerable differences between the species of Mammals that have been studied, as has been pointed out by Chr. Smith in her valuable paper on the development of the carotid body.

My observations on mammalian embryos are generally in agreement with those of Boyd in the human embryo. The carotid body appears as a mesodermic thickening in the bifurcation of the carotis communis, it surrounds the carotis interna (Plate I, fig. 2 and Plate II, fig. 2), but in later stages separates itself from the wall of this artery. In the rabbit, much less in the Marsupialia, it can be observed that a considerable number of small cells closely resembling the rudimentary cells of the cervical sympathetic ganglia arrive in the carotid body and spread in the outer layer of this organ (Plate I, fig. 2, *S.C.*). These cells are in relation with nerve fibres (Plate I, fig. 2, *S.F.*) from the superior cervical ganglion and their sympathetic origin cannot be doubted. Up to the latest stages I have been able to investigate, these cells remain in a rudimentary condition, as also do those found in the cervical ganglion. They are probably the same elements that differentiate later as chromaffin cells, but we must admit another possibility of evolution. If the elements of the carotid body become, as supposed by de Castro, receptive cells, it may be that these rudimentary cells differentiate as the elements of the central parts of the sensitive corpuscles that, following certain authors, are derived from Schwann's cells.

In the present state of my researches, it is impossible for me to indicate more precisely the significance of this remarkably constant organ of the mammalian body. But I must emphasise this very important fact that, in the bats which possess such a considerable paraganglionic system, the carotid body has apparently nothing to do with these paraganglia. The cells forming this body are quite rudimentary elements that appear as the result of a cellular



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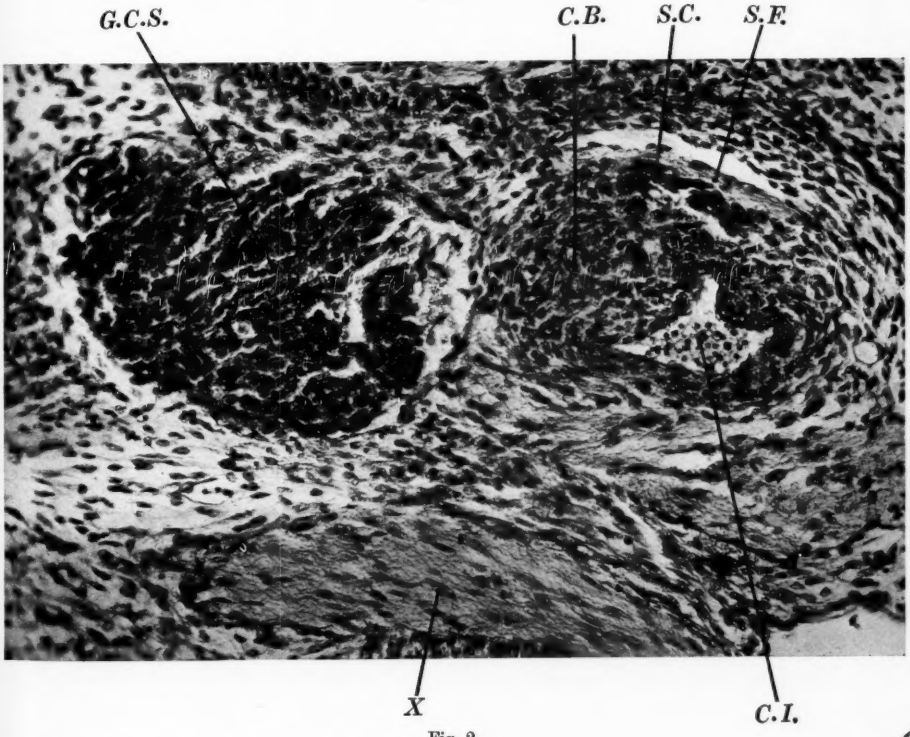

Fig. 2.

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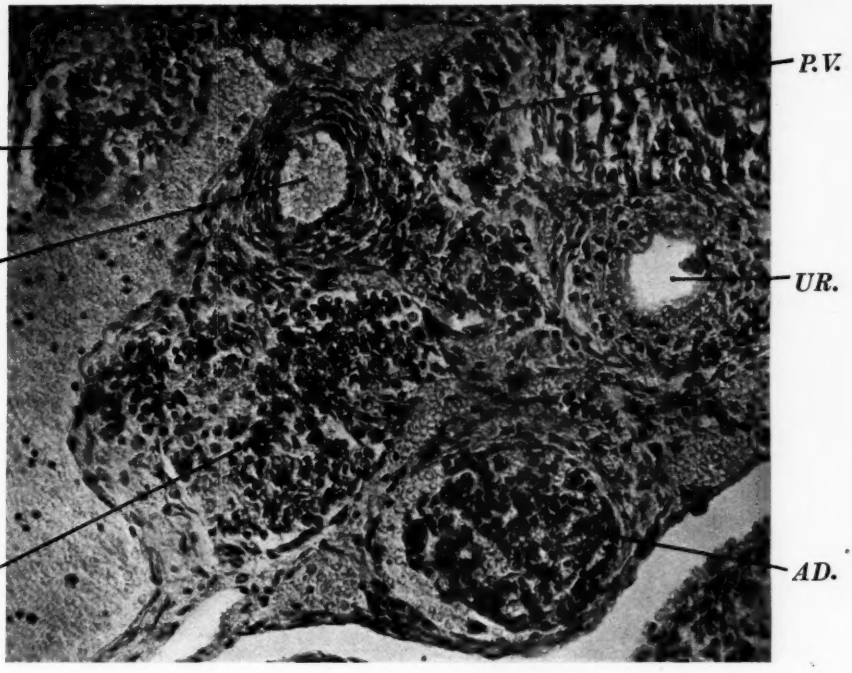

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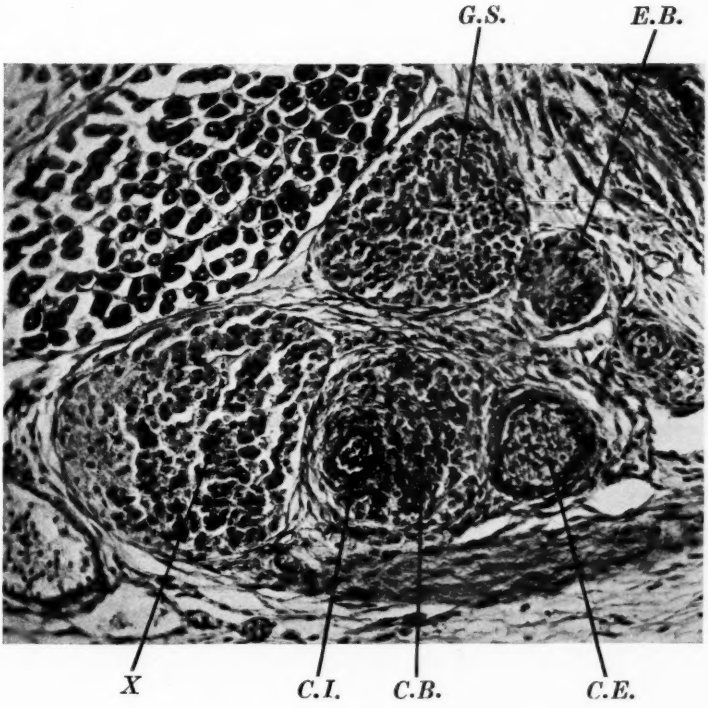

Fig. 2.

condensation in the wall of the carotid. Its structure does not support a common origin with the paraganglionic tissues.

It is evident that my studies are as yet very incomplete; other stages, especially the more advanced, must be investigated, and the examination of the adult structure is absolutely necessary.

I am much indebted to Mr F. J. Pittock, of the Department of Anatomy and Embryology, University College, London, for the photomicrographs.

EXPLANATION OF PLATES I AND II

Plate I

Fig. 1. Transverse section, rabbit embryo. Greatest length, 14 mm., 15 days. Abdominal region. *A.M.I.* arteria mesenterica inferior; *G.S.* sympathetic ganglia in medial position; *P.G.* paraganglia with peculiar large cells. Original ×230.

Fig. 2. Transverse section, same embryo. Cervical region, showing the carotid body and the superior cervical ganglion. *C.I.* carotis interna; *C.B.* carotid body; *G.C.S.* superior cervical ganglion with small dark cells, complete absence of paraganglionic cells; *S.C.* cord of dark cells (sympathetic) which reach the carotid body with the sympathetic fibres (*S.F.*); *X*, vagus. Original ×200.

Plate II

Fig. 1. Transverse section, pouch-young, *Dasyurus viverrinus*. Greatest length, 10–10·5 mm., stage G. Abdominal region, showing the peri-aortic sympathetic mass (*S.*) and the prevertebral cords (*P.V.*). *A.* aorta; *AD.* adrenal; *UR.* ureter. Paraganglionic cells dark (cf. medullary cord of adrenal), sympathetic nerve cells clear. Original ×270.

Fig. 2. Transverse section, pouch-young, *Trichosurus vulpecula*, greatest length, 16 mm., showing the carotid body. *C.B.* carotid body and *C.I.* carotis interna; *C.E.* carotis externa; *E.B.* epithelial body; *G.S.* superior cervical ganglion; *X*, ganglion and trunk of vagus. Original ×200.

OBSERVATIONS ON THE STRUCTURE OF THE UTERUS MASCULINUS IN VARIOUS PRIMATES

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Recent work on male mice (e.g. Lacassagne, 1933; Burrows and Kennaway, 1934) and on male monkeys (Parkes and Zuckerman, 1935; Courrier and Gros, 1935) has shown that rudimentary structures presumably derived from the Müllerian ducts respond to the female sex hormone, oestrin, in the manner characteristic of functional organs of the female (e.g. vagina) with a similar embryological origin. In the monkey the main structure concerned is the uterus masculinus. This embryological rudiment is found, in varying forms and in different degrees of development, in most Mammals. Its comparative morphology has, however, attracted relatively little attention, though two studies have been recently made by Hütt (1926–7) and Swoboda (1929). So far as the Primates are concerned, neither of these authors does much more than mention the fact that some members of the order possess a uterus masculinus. For reasons set out in the conclusion to this paper, the prostatic utricle of monkeys and apes is of some significance from the clinical point of view, and accordingly the following study of its comparative anatomy was undertaken.

While the existence of a uterus masculinus in Man was recognised at least as long as 300 years ago, its occurrence in monkeys seems to have remained unrecorded until the publication of Leuckart's papers in 1847 and 1852. Leuckart's observations on the distribution of the organ in Primates are still the fullest yet published. He records its existence, without providing histological details, in the following species: *Macaca irus*, the common macaque; *Macaca nemestrina*, the pigtailed macaque; *Mandrillus sphinx*, the mandrill; *Papio porcarius*, the Chacma baboon; *Hapale jacchus*, the marmoset; and a form described as *Pithecus troglodytes*, presumably the chimpanzee. Heller and Sprinz (1921) have recently added some observations on the utricle in an unnamed species of langur (*Presbytis*) and in an unnamed species of capuchin (*Cebus*), while accounts of the organ in the spectral tarsier (*Tarsius spectrum*) and in the tree-shrew (*Ptilocercus lowii*) have been published by Woollard (1925) and Le Gros Clark (1926) respectively. The tree-shrew's inclusion in our

series is justified in view of the animal's undoubted Primate affinities (see Le Gros Clark, 1934).

Most of the observations recorded in this paper have been made on material collected during the course of routine anatomical examination of animals that died in the London Zoological Society's Gardens between 1930 and 1932. All specimens were sectioned, some serially, and stained with Meyer's haemalum and eosin.

HISTOLOGICAL OBSERVATIONS

Tupaioidea

Ptilocercus lowii: the pen-tailed tree-shrew.

The material available for study comprised serial cross-sections of the urogenital tract of an adult male. Le Gros Clark's (1926) description of the utricle is as follows: "The uterus masculinus is a simple piriform sac 5 mm. in length. It extends up the posterior aspect of the prostate and the neck of the bladder to about the same height as the seminal vesicles. Below, it narrows down to open into the urethra. The mucous membrane lining of this structure is covered with columnar epithelium and thrown into complicated folds. It should be noted that neither the vas, the duct of the vesicular gland, nor the uterus masculinus passes through the substance of the prostate."

The utricle in this species is thus unlike the corresponding organ of Man and monkeys in being more or less unattached to surrounding structures. It has a relatively thick fibro-muscular wall, and its mucosa, as Le Gros Clark has described, is thrown into complicated folds, which form crypts and glands. These folds resemble the folds of the human Fallopian tube (Plate I, fig. 2). Their delicate supporting tissue is well vascularised, and characterised by spindle-shaped nuclei. The preparations occasionally also show stromal collections of large and more compact cells; these may, however, represent tangential sections of the walls of glands.

The epithelium is tall columnar, uniformly single-layered, and apparently non-ciliated (Plate IV, fig. 3). The nuclei are basally disposed, and the superficial two-thirds of the cell bodies are clear. Scattered in the epithelium are typical goblet cells, and numerous droplets of secretion are to be seen within the crypts and glands. It is of interest that the utricular epithelium of the tree-shrew resembles the typical prostatic epithelium of the Pithecoidea more closely than does any other epithelium of its urogenital tract, including even that of its prostate.

At its extreme cranial end, the lumen of the uterus masculinus is somewhat compressed dorso-ventrally, and is represented by a series of short glandular tubules (Plate I, fig. 1). The sac opens on a prominent colliculus seminalis, which is covered by transitional epithelium many layers deeper than that of the urethra generally. The epithelial folds of the utricle are carried down into its wide mouth, whose rim is marked by a sharp line of junction of utricular and urethral epithelium (Plate I, fig. 4).

Le Gros Clark has drawn attention to a small isolated lobule of the prostate lying outside the prostatic capsule, and in close association with the uterus masculinus and seminal vesicles (Plate I, fig. 3). Its topographic relations suggest that this part of the prostate of the tree-shrew is homologous with the prespermatic or middle lobe of the prostate of higher Primates.

Lemuroidea

Lemur catta: ring-tailed lemur. **M. 166.**

The animal was a fully mature male.

Serial cross-sections of the neck of the bladder and of the accessory reproductive glands were studied closely, but no trace of a uterus masculinus was found. The colliculus seminalis is very prominent, and its transitional epithelium much folded, but none of the crypts so formed is sufficiently well defined to merit recognition as a utricle. As is well known, there is no common ejaculatory duct in this species.

There is no mention of a uterus masculinus in any of the several monographs on the Lemuroidea that we have consulted. Leuckart (1849–52) specifically states that the organ is absent in *Stenops tardigradus* (=*Nycticebus coucang*) and doubts its presence in *Lemur albifrons* (a subspecies of *Lemur fulvus*).

Tarsioidea

Tarsius spectrum: the spectral tarsier.

The material studied comprised both serial cross-sections and serial longitudinal sections of the urogenital tracts of two adult males. The former set was that used by Woollard in his general anatomical study of the species (1925). The latter was prepared from a specimen kindly given us by Prof. Le Gros Clark.

The utricle is a blind and narrow flask-like diverticulum opening on the surface of the colliculus seminalis at about the level of the mouths of the common ejaculatory ducts (Plate I, fig. 5). Its length is 600 μ and its greatest diameter barely 50 μ in the fixed preparations. It has no glandular offshoots, and, as Woollard noted, it is lined by transitional epithelium. There is practically no utricular lumen to the specimen that was sectioned longitudinally.

A "prespermatic lobe" is present in the upper part of the prostate. It is formed by bilateral medial extensions of prostatic tissue which all but meet each other in the mid-line ventral to the lower ends of the seminal vesicles, the vasa deferentia, and the common ejaculatory ducts.

Pithecoidea

The general relations of the prostatic structures are the same in all the following species of Primates, and, with the one exception that prostatic glands are not developed ventral to the urethra, are the same as in Man.

Div. *Platyrrhini*

Hapale jacchus: the common marmoset. M. 195.

The specimen available for study was an adult male (body weight 272 gm.) that died of helminthiasis. Sperms were present in the vasa deferentia, seminal vesicles, and prostatic urethra.

The prostate is a compact organ, traversed ventrally by the urethra, and somewhat bean-shaped on cross-section. The uterus masculinus measures no more than 0·6 mm. in the fixed preparations. Its relatively extensive mouth is a median slit on the summit of the colliculus seminalis (Plate II, fig. 4). The lumen of the diverticulum in the region of its opening is triangular in sagittal section. Immediately cranial to this level, the utricle is very narrow from side to side, but fairly long dorso-ventrally (Plate II, fig. 3). Still higher its ventral wall expands laterally, and thus the utricle assumes the form of the letter T on cross-section. Still more cranially it is represented by a coronal crossbar with two sagittal dorsal extensions (Plate II, fig. 2). It ends blindly in a series of separate glandular tubules (Plate II, fig. 1).

The utricular epithelium is cuboidal, from one to two layers deep, and closely resembles that of the ejaculatory ducts (Plate IV, fig. 4). The transitional epithelium of the colliculus seminalis invades the uterus masculinus, which is filled with partly inspissated secretion, for a short distance.

The utricular stroma is far more cellular than that of the rest of the prostate. The stromal cells are very tightly packed. Both the uterus masculinus and the ejaculatory ducts are insulated from the rest of the prostate, and to some extent from each other, by definite layers of fibro-muscular tissue.

Div. *Catarrhini*

Macaca mulatta: rhesus macaque.

The material available for study comprised complete serial sections of the prostatic region of two immature rhesus monkeys, as well as occasional sections of several others. A description of the histology of the entire prostate has been published elsewhere (Parkes and Zuckerman, 1935*a*).

The utricle extends from the cranial lobulated part of the prostate to the upper part of the crista urethralis, which is confined to the distal half of the prostate. Its coronally disposed and somewhat semilunar mouth opens at the same level as do the common ejaculatory ducts.

Except at its extreme cranial end and at its mouth, the utricle is T-shaped on cross-section, its lumen projecting dorsally in the mid-line in the form of a narrow slit (Plate IV, fig. 1). Sometimes this dorsal projection is represented by a non-canalised bar of epithelial cells. The epithelium is cuboidal, as a rule from one to two layers deep and regularly disposed. In practically none of the sections was there any evidence of glandular budding from the main lumen. As in other Primate species, the utricular stroma is more cellular and vascular

than that of the rest of the prostate, from which it is insulated by a distinct fibrous "capsule", projections of which to some extent also separate the utricle from the common ejaculatory ducts.

None of the animals examined was mature, but in view of our findings regarding both adult specimens of other species of macaque and adult baboons (see below), it would seem unlikely that the utricle of the rhesus would be significantly different in adult life.

Macaca nemestrina: pig-tailed macaque. **M. 186.**

The specimen available for study was a fully mature male that had been shot in the field. The form of the utricle is practically the same as that of the rhesus, from which it deviates only in certain minor details. The epithelium is columnar, with relatively large nuclei, and closely resembles that of the ejaculatory ducts. The upper blind part of the utricle shows some shallow glandular budding from the main lumen, which is filled with coagulated secretion.

The fibro-muscular capsule of the utricle and ejaculatory ducts is very well shown (see Plate III, fig. 1).

Macaca irus: common macaque. **M. 164.**

This specimen, like the pig-tailed macaque, had been shot in the field, and unfortunately the prostate proved to be poorly fixed. The structure of the uterus masculinus does not, however, appear to be different from that of the pig-tailed macaque.

Papio papio: guinea baboon. **M.M. 22.**

The specimen available for study was an immature male. Its utricular epithelium is from one to two layers deeper than that of the rhesus macaque. Otherwise the uterus masculinus shows no significant differences from that of the macaque.

Papio hamadryas: hamadryas baboon. **M. 188, 191.**

The specimens studied were taken from fully mature adult males of about 20 kg. in weight. The form of the uterus masculinus is the same as that of the rhesus, with the exception that there is a greater tendency to glandular budding from the main lumen (Plate III, fig. 2). The epithelium is pseudo-stratified columnar, and the free margin of the cells is covered with secretion (Plate III, fig. 5).

The utricular capsule and stroma are the same as in the macaque.

Cercopithecus mona: mona monkey. **M. 236.**

The specimen studied was taken from a fully mature male, 5 kg. in weight. The material was fixed immediately after death, and active sperms were found in the vasa deferentia and in the lower part of the seminal vesicles.

The general form of the utricle is the same as that of the rhesus monkey (Plate III, fig. 3). The fibrous capsule separating the utriculus from the rest

of the prostate and from the ejaculatory ducts is exceptionally well marked. The utricular stroma is very vascular and somewhat dense and fibrous.

There are numerous and relatively extensive glandular offshoots from the main T-shaped lumen, and both these and the main lumen contain coagulated secretion. The epithelium is pseudo-stratified columnar, and the basement membrane is not well defined (Plate V, fig. 1).

The utricle in this species of *Cercopithecus* differs conspicuously from that of the macaque in its greater glandular development. A similar appearance is shown by the uterus masculinus of the langur (*Presbytis*) figured by Heller and Sprinz (1921).

Cercopithecus aethiops pygerythrus: Mozambique vervet monkey. M. 182.

The specimen studied was taken from a fully mature male, 6 kg. in weight. As in other Primate species, the utricle is enclosed in a common fibrous capsule with the ejaculatory ducts, but separated from them by distinct layers of fibro-muscular tissue.

The utriculus is markedly "uterine" in appearance (Plate III, fig. 4). It is a highly glandular structure, and the many branched tubular glands, opening into the main lumen, penetrate deeply into the utricular stroma, which is very vascular. The stroma cells resemble those of an involuted Primate uterus. They are densely packed and their nuclei are often spherical and polygonal, in contrast to the spindle-shaped nuclei of the typical fibrous tissue of the rest of the prostate. The glandular epithelium is characteristically single-layered columnar with basal nuclei (Plate V, fig. 2). The surface epithelium lining the main lumen is generally not as deep as that of the glands. The basement membrane shows clearly in many areas.

Pan satyrus: chimpanzee. M. 180.

The specimen studied was taken from an immature male, 13·5 kg. in weight, that died of broncho-pneumonia. The true prostatic glands are identical with those of the immature rhesus monkey.

The utricle is a small diverticulum, less regular in shape than that of the macaque or baboon, and with a wider lumen, which shows numerous glandular offshoots. The stroma is loose and cellular. The glandular and surface epithelium is pseudo-stratified columnar (Plate IV, fig. 2). There is no evidence of secretion.

Like the uterus masculinus of the mona and Mozambique monkey, that of the chimpanzee differs from that of the other catarrhine monkeys studied in its essentially glandular appearance.

DISCUSSION

The data recorded above show that there is considerable variation in the degree of development of the uterus masculinus in sub-human Primates. The structure may appear, for example in the young rhesus monkey, as a diverti-

culum lined by a single layer of cuboidal cells, or it may be represented by a glandular organ of uterine appearance, as in the Mozambique monkey. Vintemberger (1926) has convincingly demonstrated that the form of the human utricle varies between two well-defined types: (1) a diverticulum with a wide lumen, and an obvious opening on the crista urethralis, but with poorly developed glands, and (2) a highly glandular organ, the individual glands not unlike those of the uterus, with a narrow central lumen and often with a closely concealed mouth, which may even open into one of the ejaculatory ducts.[1] As a general rule the highly glandular human utriculus is not seen before puberty, but the two main types can usually be distinguished from each other earlier on, and sometimes even at birth. Meyer (1909) has given a description of the utriculus of a full term foetus in which the glandular development of the utricle, while confined to the boundaries of the prostate, is as marked as the most glandular adult utricle figured by Vintemberger.

The homology of the uterus masculinus is by no means established. It is generally assumed to represent the uterus and vagina. There could be little doubt about the correctness of this homology in such species as the beaver (Leuckart, 1849–52), in which the uterus masculinus is said to be normally represented by a bicornuate structure almost identical in appearance with the female reproductive tract, or in certain abnormally developed cases in Man (for example, that recorded by Primrose, 1899), in which an obvious vagina passes through the prostate to open into an equally obvious uterus lying immediately behind the base of the bladder. When, however, the fully developed structure such as the above is represented by only a blind and non-glandular diverticulum lined by a low epithelium, as in the rhesus monkey, there seems good reason for the by no means uncommon opinion that the organ should be properly styled a *vagina masculina*, to signify that it is homologous only with the vagina.

The problem of the proper homology of the Primate utriculus is of far more than academic interest. The utriculus of the rhesus monkey reacts to oestrin by epithelial growth and cornification (Parkes and Zuckerman, 1935). The complete similarity of this response to the vaginal oestrin reaction can leave little doubt that the utricle of the rhesus monkey, as its histological appearance would suggest, represents only a vagina. On the other hand, if histological appearances are to be trusted, and the utricular glands shown by some Primate species—including Man—are actual homologues of uterine glands, it would be expected that their response to the unopposed action of oestrin would be cystic hyperplasia, such as occurs in the female Primate uterus in similar circumstances (Zuckerman and Morse, 1935). An extensive cystic hyperplasia of a true uterus masculinus would produce a histological appearance of the "middle lobe" not unlike that of the enlarged glandular prostate of clinical

[1] In Man, as in other Primates, a common fibro-muscular capsule separates the uterus masculinus and ejaculatory ducts from the true prostatic glands, so that there is little possibility of confusing the utricular glands with those of the prostate.

medicine, a condition whose origin and early stages are altogether obscure. For this reason the question of the homology of the uterus masculinus of Primates needs to be considered closely.

The view that the normal utricle in Man is the homologue of the vagina, or the vagina and uterus together, is fundamentally based on the assumption that both structures develop from the caudal part of the fused Müllerian ducts. This assumption, though accepted as valid by text-books of embryology, has been assailed by several recent studies, and many workers now believe that the vagina develops at least partly from cells derived from the urogenital epithelium.[1]

It is generally agreed that early in development (about 30 mm.), the Müllerian ducts come into contact, at Müller's tubercle, with the epithelium of the urogenital sinus, into which, according to some authors (e.g. Wood-Jones, 1904), the conjoined ducts at this time actually open. All investigators describe the subsequent occurrence of a process of obliteration of the lumen of the fused ducts, beginning distally and proceeding cranially, with the consequent appearance of a uterovaginal cord of cells canalised only in its upper part. Such a process of obliteration occurs in both sexes, in both of which the same uncertainties in our knowledge of the later developmental processes apply. These uncertainties mainly concern the derivation of the solid cord of cells that makes up the lower part of the uterovaginal canal, and which is the anlage of the vagina. Bloomfield and Frazer (1927) and Hunter (1930), agreeing with the older opinion, hold that all these cells in the female are definitely Müllerian in origin. Evatt (1909), Meyer (1909), Alesio (1929) and Vintemberger (1926), on the basis of their findings, state a corresponding view for the male. On the other hand, Spuler (1930) and Vilas (1932) present evidence that the cells are derived from the sinus epithelium over Müller's tubercle. Their view is that the caudal part of the uterovaginal canal retrogresses, and that the canal retains connection with the tubercle only through the medium of a cord of cells proliferated from the sinus. Vilas (1933) has also described an identical process as occurring in the male, whose Müllerian ducts, he believes, as a rule atrophy completely. In this his observations appear to tally with those of Perna (1924). In support of this view, it may also be noted that Meyer (1909), whose studies, as noted above, led him to the general conclusion that the uterus masculinus is derived from the caudal part of the Müllerian ducts, also described certain cases in which sinus epithelium invaded the foetal utriculus masculinus. The opinion stated by Koff (1933), on the basis of a careful investigation of the derivation of the solid vaginal plate, is an intermediate one. According to him about the lower fifth of the vagina is derived from "sino-vaginal" bulbs proliferated from the squamous epithelium over the site of Müller's tubercle,

[1] For the purpose of the present discussion, we may omit reference to the still occasionally reiterated view—e.g. Mijsberg (1924, 1925), Kempermann (1931, 1934)—that the terminal parts of the Wolffian ducts are also concerned in this development. For criticisms of this opinion see Bloomfield and Frazer (1927), Hunter (1930), Vilas (1932) and Koff (1933).

while the upper four-fifths develop from the fused and solid caudal segment of the Müllerian ducts. It may be noted here that all observers agree that the unfused cranial parts of the Müllerian ducts and the upper part of the utero-vaginal canal atrophy in the male foetus.

In spite of the fact that it is no longer certain that the vagina and uterus masculinus take origin only from the caudal part of the Müllerian ducts, it is safe to assume that the two are homologous organs in view of their similar derivation from a solid cord of cells whose development appears to be the same in both sexes. This conclusion, however, leaves unsettled the question of a possible involvement of a uterine element in the Primate uterus masculinus. If we accept the opinion that the *whole* of the vagina is derived from a solid outgrowth of cells proliferated from sinus epithelium, it follows that all functional structures derived from the epithelium of the Müllerian ducts (e.g. uterus and Fallopian tubes) *ipso facto* develop glands, and the problem then is to discover whether any cells of Müllerian origin are included in the utero-vaginal cord of the male Primate. If, on the other hand, we accept the view that part of the Primate vagina is derived from the Müllerian ducts, it follows that cells derived from the latter may develop into non-glandular (i.e. vaginal) as well as glandular epithelium (i.e. uterine), and the question then is to enquire to what extent, if any, do the Müllerian tubes persist in the male.

The available embryological data do not permit a definite answer to either of these questions. As noted above, some authors regard the utricle as being entirely a derivative of the fused Müllerian ducts, while a few, like Vilas, take a contrary view, and affirm that the ducts completely atrophy in the male foetus. Vilas' observations, although more detailed and abundant than any other we know on the problem of the utriculus, do not, however, provide his conclusions with the conviction that would assure their acceptance. His interpretation is that the cranially extending cord of cells, which he regards as a derivative of sinus epithelium, finally absorbs or replaces what is left of the cells of the uterovaginal canal, which has retrogressed in both its cranial and caudal segments. The actual number of specimens on which this part of his story of the developmental process is based is, however, very small. Moreover, the ability to state that the one type of cell replaces the other, depends upon their clear histological distinction from each other, which he himself has to admit is at times "nicht genau feststellbar". It is on this issue that Koff's criticisms of Vilas' similar conclusions regarding the female are based. Koff's observations, made on more extensive material than Vilas had at his disposal, show that only the lower part of the solid vaginal plate of the female, and not the whole of the plate as Vilas assumed, is derived from sinus epithelium. In view of this consideration, and since all observers are agreed that the anlage of the utriculus is at least equivalent to the vaginal plate of the female, it therefore seems safe to conclude that the utriculus is partly derived from the Müllerian ducts. According to Frazer (1931), the vaginal or, as Koff calls them, sino-vaginal bulbs, do not develop far in the male, and it may well be therefore that

the solid vaginal plate of male foetuses includes relatively more Müllerian duct epithelium than it does in the female.

The question whether any of the cells derived from the Müllerian remains of the male Primate give rise to glands homologous with those of the uterus is more difficult to answer on the available embryological data. The balance of present evidence is that the solid vaginal plate in the female reaches only as far as the region which differentiates into the external os, or occasionally to a point about half-way up the cervical canal (Koff, 1933). On this view it would be necessary, in order to show that a true uterine element is included in the anlage of the utricle, to demonstrate a persisting canalised part of the fused Müllerian ducts at the cranial end of the solid vaginal plate of male foetuses older than approximately the 100 mm. stage (on the basis of our present knowledge of the equivalent process that takes place in the female). Occasional observations in the literature (including some of Vilas) do indeed suggest that such remains of the genital canal may be found. The question, however, requires thorough re-investigation before any conclusions can be drawn.

There are other points which may well be considered in this connection:

(*a*) If the normal non-glandular vagina lined with stratified epithelium is taken to represent the final phase of development of the solid vaginal plate, it follows that the latter alone cannot be regarded as forming the anlage of a *glandular* uterus masculinus, but that some other factor, possibly a more cranial part of the uterovaginal canal, is also concerned in the utricle's development.

(*b*) The full glandular development of the uterus masculinus, although sometimes apparent at birth, is, according to Vintemberger, a post-pubertal phenomenon as a rule. In this the utricle behaves in much the same way as the uterus of the female; uterine glands may sometimes be well developed at birth, but at other times the endometrium of the body of the uterus remains simple and almost non-glandular until puberty, when the sex-hormones begin to exercise their effects. It may well be that the glandular transformation of the uterus masculinus is also dependent on specific endocrine activity.

(*c*) As a last point in this connection it may be noted that the vaginal stratified epithelium is capable of undergoing glandular changes in certain conditions—for example, during pregnancy (Barrington, 1915; Zuckerman and Parkes, 1932), and, in the case of the immature mouse, in response to oestrin (Aberle, 1933). Even were the uterus masculinus a derivative of only the vaginal plate, it could therefore be expected to undergo glandular changes in certain endocrine conditions.

The available embryological data thus allow only tentative conclusions to be drawn regarding the inter- and intra-specific variability of the Primate uterus masculinus. The different degrees of the utricle's glandular development suggest that the Müllerian ducts undergo correspondingly varying degrees of regression during development, and that in some cases only the vaginal, in others uterine as well as vaginal, anlagen persist. The problem could probably

be settled by further embryological study. If, as is not unlikely, it proves impossible to differentiate sufficiently well by histological means between different parts of the uterovaginal canal, the question of the homology of the utricle would have to be answered in terms of its varying response to female sex-hormones.

SUMMARY

A study has been made of the uterus masculinus in a representative series of subhuman Primates.

The organ is absent in the lemur, *Lemur catta*. In the tree-shrew, *Ptilocercus lowii*, it appears as a simple, relatively independent and extensive sac, in which the mucosa is arranged similarly to that of the Fallopian tube. In *Tarsius spectrum* the utricle comprises a minute flask-like diverticulum lined with transitional epithelium, and opening on to the crista urethralis.

In the marmoset the utricle is a small but complex glandular organ, whose blind end is represented by a series of simple secretory tubules.

Among the Old World monkeys studied, the form of the utricle varies between two fairly well-defined types. In three species of macaque and in two species of baboon, the utricle appears as a simple organ with no glandular offshoots, whose lumen in cross-section is generally T-shaped, and whose epithelium may be either cuboidal or columnar. In two species of *Cercopithecus* the utricle is highly glandular, and in one of the two species typically "uterine" in appearance.

The utricle of the chimpanzee is also a glandular organ.

The anatomical findings regarding the uterus masculinus in Primates are considered in relation to our knowledge of the embryology of the organ.

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EXPLANATION OF PLATES I–V

Plate I

Ptilocercus lowii

Fig. 1. Cranial extremity of uterus masculinus, showing dorso-ventral flattening, and replacement of main lumen by separate tubular glands. × 37.

Fig. 2. Transverse section of body of uterus masculinus, showing folded mucosa. The structures on either side of the utricle are the vasa deferentia, and ventral to it can be seen prostatic glands. × 37.

Fig. 3. Immediately dorsal to a fold in the section can be seen a group of prostatic glands intervening between the urethra and the uterus masculinus. This part of the prostate may be regarded as the homologue of the prespermatic lobe of higher Primates. × 37.

Fig. 4. Mouth of the uterus masculinus, showing the transition between the utricular columnar epithelium and the transitional epithelium of the colliculus seminalis. × 155.

Tarsius spectrum

Fig. 5. Median sagittal section of uterus masculinus. × 75.

Plate II

Hapale jacchus. × 55

Fig. 1. Cranial extremity of uterus masculinus, showing discrete tubular glands.

Fig. 2. A more caudal level of the uterus masculinus showing ventral transverse bar with two dorsal sagittal extensions of lumen.

Fig. 3. A still more caudal plane of the uterus masculinus, where it is represented by a simple dorso-ventral slit.

Fig. 4. The median depression in the colliculus seminalis is the lower level of the mouth of the uterus masculinus. On either side of it can be seen the openings of the common ejaculatory ducts.

Plate III

Fig. 1. Uterus masculinus of *Macaca nemestrina*, showing the T-shaped lumen, the vascular stroma, and the fibro-muscular tissue insulating the utricle and ejaculatory ducts from the rest of the prostate and to some extent from each other. The two peripheral tubules are collecting ducts of the prostate. × 45.

Fig. 2. Utriculus of *Papio hamadryas*, showing the typical cercopithecoid T-shaped lumen. × 45.

Fig. 3. Utriculus of *Cercopithecus mona*, showing the usual capsule and T-shaped umen. Note also the dense utricular stroma and the glandular offshoots from the main lumen. × 45.

Fig. 4. Utriculus of *Cercopithecus aethiops pygerythrus*. Note the organ's general uterine appearance. Numerous tubular glands can be seen ramifying in the cellular stroma. × 45.

Fig. 5. Columnar epithelium of uterus masculinus of *Papio hamadryas*. Note also the relatively non-fibrous stroma. × 190.

Plate IV. × 140

Fig. 1. Uterus masculinus of *Macaca mulatta*. Note the double layer of epithelium and the highly cellular stroma.

Fig. 2. Uterus masculinus of *Pan satyrus*, the chimpanzee, showing the pseudo-stratified columnar epithelium and tubular offshoots from the main lumen. In the lower part of the figure can be seen a tubular gland lying in the utricular stroma and cut off from the main lumen.

Fig. 3. Uterus masculinus of *Ptilocercus lowii*, showing a much folded tongue of mucosa covered by a single layer of high columnar epithelium.

Fig. 4. Uterus masculinus of *Hapale jacchus*, showing incipient division of main lumen into separate tubular glands.

Plate V. × 190

Fig. 1. Uterus masculinus of *Cercopithecus mona*, showing pseudo-stratified columnar epithelium and glandular offshoots from the main lumen. The basement membrane is obscure in places, and the stroma is highly vascular.

Fig. 2. Uterus masculinus of *Cercopithecus aethiops pygerythrus*, showing the tubular glandular offshoots from the main lumen. A gland can be seen in the right-hand corner, lying deeply in the highly cellular stroma.

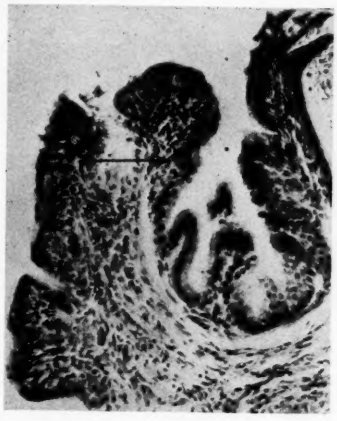

Fig. 4.

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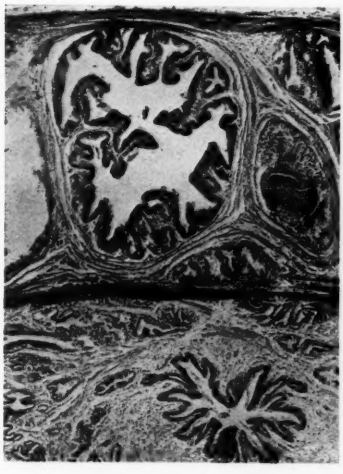

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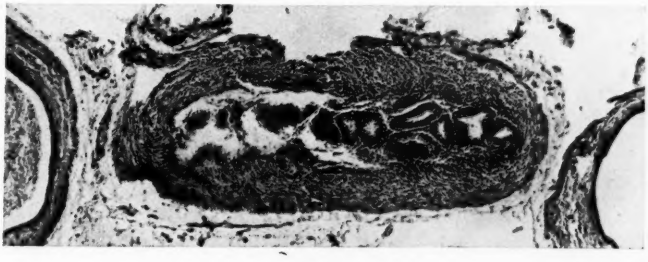

Fig. 1.

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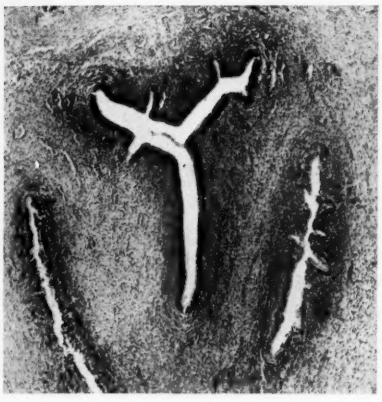

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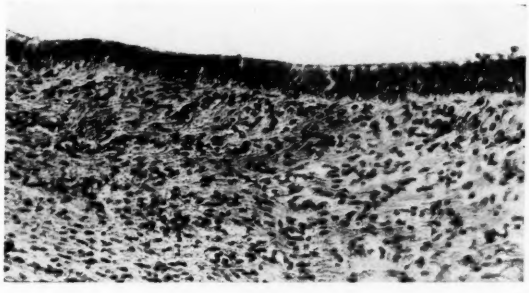

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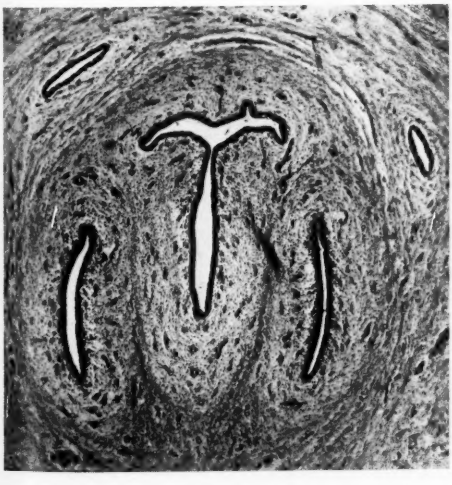

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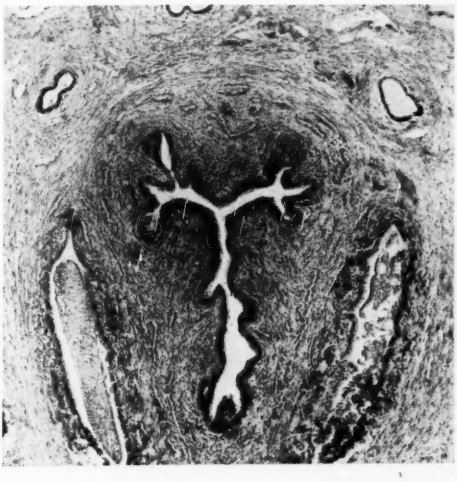

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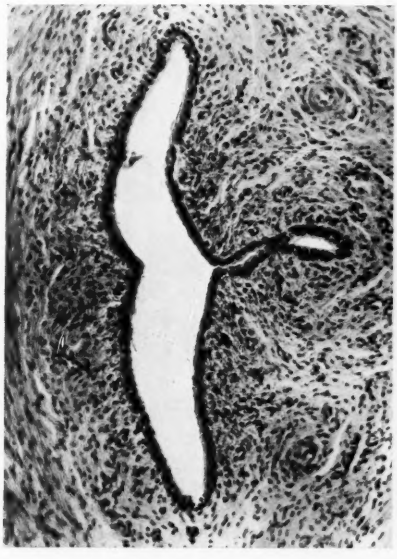

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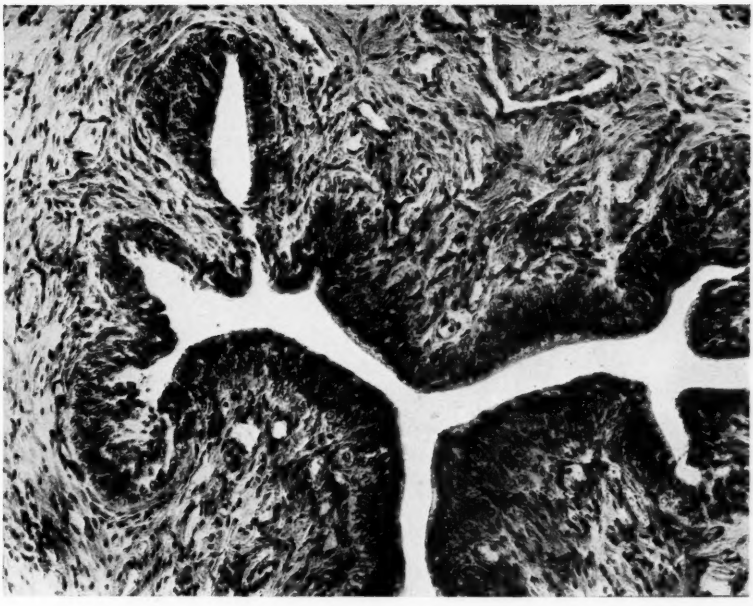

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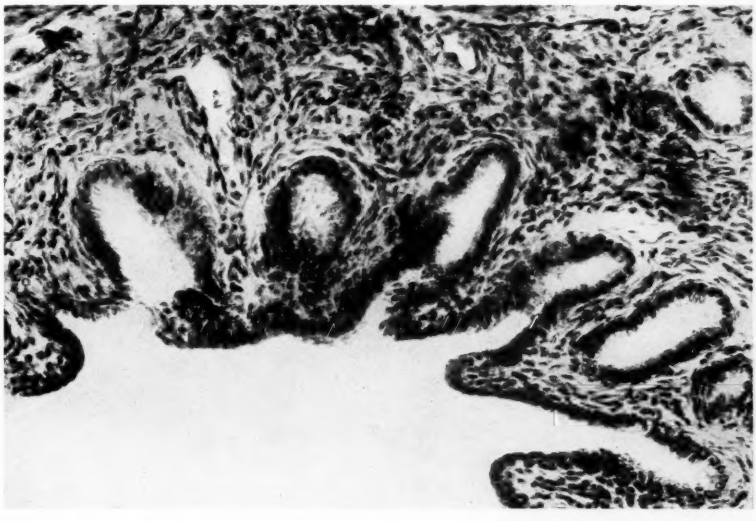

Fig. 2.

THE SENSITIVITY OF THE NEW-BORN MONKEY TO OESTRIN

By S. ZUCKERMAN[1] and G. van WAGENEN

From the Department of Physiology and the Department of Gynaecology and Obstetrics, Yale University School of Medicine

In 1904 Halban suggested that sex hormones present in the tissues of pregnant women are able to permeate the placenta and affect the reproductive organs of the foetus. Evidence supporting this view is to-day strong, and comprises data regarding size changes in the male and female reproductive organs during later foetal and early post-natal life, and assays of the hormone content of the blood and urine of new-born infants (for recent reviews of the subject see Scammon (1926), Neumann (1930), and Engle (1932)).

The question of the permeability of the placenta of other mammalian species is still in dispute. Courrier (1924) has reported experiments in which the vagina and uterus of new-born guinea-pigs had undergone growth in response to oestrin injected into the mother animal towards the end of term. He has also brought forward evidence to show that the genital tract of the new-born guinea-pig may be correspondingly active under normal conditions as well (1928, 1930), and together with Gros (1932) he has presented similar observations for the cat. Several workers have failed however to corroborate his findings (Allen, Francis and Craig, 1925, using rats; Loeb and Kountz, 1928, using guinea-pigs), and Parkes and Bellerby (1926) have found that oestrin is unable to exercise any obvious effect on the reproductive organs of new-born mice.

The present paper is concerned with observations which bear on the general question of the permeability of the placenta and which show that the new-born monkey is sensitive to oestrin.

THE NEW-BORN MALE RHESUS MONKEY

Wislocki (1933) has pointed out, on the basis of an examination of fixed material, that the scrotum of the new-born rhesus macaque is swollen and oedematous. We have been able to corroborate this observation on three animals born in our laboratory, finding in addition that the swelling disappears within a week. Wislocki has also collected suggestive data supporting the view, advanced by Hartman in 1928, that the fold of the skin which passes transversely across the symphysis pubis in young female rhesus monkeys is homologous with the scrotum of the male, and in considering the resemblance of the

[1] At the time of the investigation, a Rockefeller Research Fellow.

male infantile scrotum to the feminine "scrotal fold", he comes to the conclusion, partly on the basis of the experimental findings of Engle (1932 *a*), "that the anterior lobe hormone or the anterior lobe-like substance of urine"—presumably arising in the maternal organism—is responsible for the oedema and swelling of the scrotum of the new-born macaque. He points out, however, that it would be of interest to discover whether or not oestrin can induce scrotal swelling in the new-born animal. The experiment reported below gives a positive answer to this question.

The animal investigated was a young male rhesus born on 12 May, 1933. The natal scrotal oedema had disappeared by 19 May, and on that date the testes, which felt about the size of a pea, were confined to the upper part of a lax scrotal sac. The animal had an accessory nipple below and medial to the normal left nipple.

The first series of aqueous oestrone (keto-hydroxy-oestrin) injections lasted from 18 May to 29 June, 1933 (43 days), a total of 8250 rat units being injected.

No change was noted in the perineal area until the close of the second week of injections, when swelling, eversion, and increased coloration of the margins of the anus became apparent. The response soon spread to other parts of the animal's hind quarters, and by 26 June the whole of the buttock region was thrown into a series of indurated rolls on which the hair follicles stood out prominently. The affected area extended laterally from the buttocks to the flanks, upwards on to the back and around the base of the tail, which was converted into concentric circular rings of swelling, and downwards along the postero-lateral and postero-medial aspects of the thighs. Even the callosities were corrugated. The least affected area was the scrotum itself, which by the end of a month of injections was but little more prominent than it had been at the beginning. It did, however, show definite swelling and oedema by the end of the series of injections. The affected regions, as they appeared one month after the beginning of the experiment, are shown in Plate I, figs. 1 and 2, and as they appeared at the close of injections, a week after this date, in Plate I, fig. 3.

The nipples, including the accessory one, responded to the course of injections by increasing in size and becoming more intensely coloured. The changes are indicated in the figures.

The young animal's testes were removed on 23 August, 1933. Plate I, figs. 4 and 5, shows the appearance of the scrotal and perineal areas on 6 September, after healing had occurred. It will be seen that there is practically no swelling of the scrotal skin.

A second series of oestrone injections was begun on 8 September and continued to 20 September (13 days), a total of 3300 rat units being injected.

At the end of this course there was little change in the region previously affected.

Accordingly a third series of injections was begun 8 days after the end of the second, and continued for 6 days. In addition to the usual aqueous solution

an oily preparation of oestrone was also injected, a total of 3300 rat units being administered in all. The response to this series of injections was much more definite than that of the second series. Thickening and corrugation of the perineal and scrotal skin began soon after the first injection and continued until a week following the last. The scrotal response was much better than it had been during the first course of injections, when the testes were present.

On 10 October, a week after the last injection of the third series, a single dose of the oily preparation of oestrone, equivalent to 2500 rat units, was injected. The swelling increased greatly as a result of this injection. The final response is indicated by Plate I, figs. 6, 7, 8. The swelling of the scrotal skin is well shown in fig. 6.

THE NEW-BORN FEMALE RHESUS MACAQUE

Swelling of the sexual skin was noted in a young female rhesus macaque at the time of its birth on 27 November, 1933. The swelling was puffy, but fairly well defined, and limited mainly to the "scrotal folds". These extended transversely across the middle third of the symphysis pubis. The praeputium clitoridis was involved in a caudal extension of the swelling. Laterally, the scrotal folds, which extended along the medial aspect of the thighs, reached as far as the popliteal fossae, thus demarcating the full normal sexual-skin area of the mature animal of the species. The amount of swelling soon decreased, but the region remained prominent for a considerable time.

The sexual skin of this monkey thus gave unmistakable evidence of the activity of oestrin, which in all likelihood was of maternal origin. The question of the young animal's sensitivity to the hormone was not tested further.

Oestrone was, however, injected, with the usual results, into a $6\frac{1}{4}$ months old female rhesus monkey, also bred in our laboratory. In spite of the absence of any sexual-skin swelling, the limits of the scrotal folds could be clearly defined in this animal at birth. 3150 rat units of oestrone were injected over a period of 14 days. Swelling of the sexual-skin area began on the fourth day of injections, and extended over the perinaeum, on to the flanks, and down the thighs. The swelling and coloration also extended to the base of the tail, which was thrown into a series of rolls. The response was very pronounced.

Uterine bleeding began 8 days after the cessation of injections and continued for 5 days. Three weeks passed before the swelling completely disappeared.

SUMMARY AND CONCLUSION

Swelling of the external genitalia and immediately surrounding skin of both male and female new-born rhesus monkeys has been observed under normal conditions. The inference is accordingly made that the placenta of the rhesus is permeable to oestrin. Experiments are also reported showing that oestrone injected into a new-born male and an infant female rhesus monkey caused swelling of the genital and circumgenital skin.

The oestrone used in this study was provided by Dr Oliver Kamm of the Parke, Davis Company, and by Dr Gregory Stragnell of the Schering Corporation, to both of whom we wish to express our thanks.

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EXPLANATION OF PLATE I

Fig. 1. Photograph showing prominence of nipples and absence of scrotal swelling in a new-born rhesus monkey following oestrone injections.
Figs. 2 and 3. Photographs showing swelling of skin of buttock region in response to oestrone.
Fig. 4. Photograph showing normal quiescent condition of scrotal skin of new-born rhesus monkey following castration.
Fig. 5. Photograph showing non-swollen skin of buttocks following castration.
Fig. 6. Photograph showing swelling of scrotal skin of castrated new-born rhesus monkey in response to oestrone.
Fig. 7. Photograph showing swollen rolls of skin at base of tail in response to oestrone.
Fig. 8. Photograph showing swelling of skin of buttock region of castrated new-born rhesus monkey in response to oestrone.

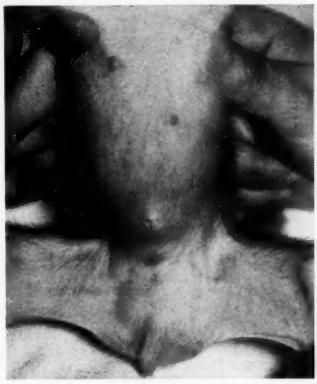

Fig. 1

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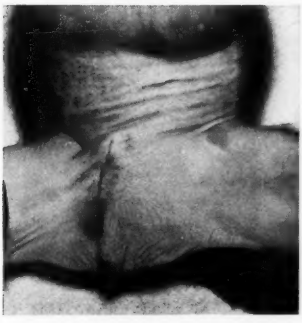


Fig. 4

Fig. 6

Fig. 5

Fig. 7

Fig. 8

ZUCKERMAN AND WAGENEN—THE SENSITIVITY OF THE NEW-BORN MONKEY TO OESTRIN

UNIV. OF MICH.

THE SUBCOMMISSURAL ORGAN AND THE MESOCOELIC RECESS IN THE HUMAN BRAIN, TOGETHER WITH A NOTE ON REISSNER'S FIBRE

By M. F. LUCAS KEENE and E. E. HEWER

London (Royal Free Hospital) School of Medicine for Women

Whilst studying the composition of the posterior commissure in numerous human foetal brains, a structure that was apparently Reissner's fibre was found in one specimen of 15 weeks. A careful search was then made for this fibre in all the material available, but remains were found in only one other specimen, a foetus of 16 weeks. This investigation necessarily included a study of those structures that are so closely related to the fibre, namely the subcommissural organ and the mesocoelic recess.

Nicholls (1) has given a full description of the development and structure of Reissner's fibre and of the subcommissural organ in Fishes, while Dendy and Nicholls (2) describe these structures and the mesocoelic recess in certain Mammals.

(*a*) *Subcommissural organ and mesocoelic recess.* According to Dendy and Nicholls (2) the subcommissural organ is "primarily made up of two bands of columnar epithelium, usually more or less completely united together in the form of a groove; but, whereas it remains throughout life in a well developed condition in all the lower vertebrates, in man...it becomes reduced in the adult to a mere vestige sunk in the brain tissue at the back of the posterior commissure". In a human foetus of 5 months these authors describe a well-developed subcommissural organ which began cephalically in the floor of the infrapineal recess and becoming clearly paired passed caudally in relation to two small grooves round the curve of the posterior commissure: at the hinder end of the commissure the two grooves united and were invaginated into the roof to form the mesocoelic recess, which tunnelled forward into the brain tissue and had a blind termination. The vestige of this recess, with no opening, was all that these workers found of the subcommissural organ in an adult human brain.

(*b*) *Reissner's fibre.* The fibre is described by Nicholls (1) as arising in Fishes from near the anterior border of the subcommissural organ in the infrapineal recess and lying closely against the surface of the organ near the middle line: it receives fresh accessions of fibrillae along the whole length of the posterior commissure, and then passes caudally stretching like a thread across the fourth ventricle and through the spinal canal to emerge ultimately at the posterior neuropore.

This fibre is said to be present only in tailed animals (3), although it occurs in all vertebrate classes (4); it has been described in Primates (*Macacus*) by Horsley (5), but not (as far as the authors know) in the human (3).

Various functions have been assigned to Reissner's fibre. Sargent (6) regarded it as a nervous structure and directly concerned with optic reflexes. There is, however, no evidence that it is nervous in nature (5), and Dendy (7) suggested that it might in part help in the circulation of the cerebro-spinal fluid, and, in addition, as it is an elastic thread which "springs" when cut, it probably exists during life under considerable tension, and together with the subcommissural organ it may form part of an apparatus for regulation of flexure of the body. Winkler (3) suggests that the impulses reaching the subcommissural organ can be transmitted thence to the habenular ganglion by the posterior commissure and the pedunculi conarii, an efferent path being then available through the fasciculus retroflexus of Meynert to the region of the red nucleus.

MATERIAL

The material on which this paper is based consists of thirty-one specimens in which serial sections of the brain are available; they range in age from a 10-mm. embryo up to an infant of 9 months. The following list gives the age and method of staining of each specimen:

Serial no.	Age	Staining
2186	10-mm. embryo	H. and B.S.
2122	12-mm. embryo	H. and B.S.
2325	12·5-mm. embryo	H. and B.S.
2329	16-mm. embryo	R.
2326	25-mm. embryo (7½ weeks)	H. and B.S.
2297	8-week embryo	H. and B.S.
2198	37-mm. embryo (8½ weeks)	H. and B.S.
2339	10-week embryo	Picrocarmine
2321	12-week foetus	H. and B.S.
76	12–14-week foetus	H. and B.S.
2333	13-week foetus	H. and B.S.
2331	14-week foetus	R.
62	15-week foetus	R.
1163	About 16-week foetus	W.P.
2332	16-week foetus	R.
2306	16–18-week foetus	Bielschowsky
2220	16–18-week foetus	H. and B.S.
2250	16–18-week foetus	H. and B.S.
2231	18-week foetus	H. and B.S.
2341	18-week foetus	H. and B.S.
64	18-week foetus	R.
2275	28-week foetus	H. and B.S.
1160	36-week foetus	W.P.
2219	Full-time foetus	H. and B.S.
1157	Full-time foetus	W.P.
2338	3-day infant	W.P.
2312	3-month infant	W.P.
2300	3-month infant	W.P.
2301	6-month infant	W.P.
1164	8-month infant	W.P.
2296	9-month infant	W.P.

Note. H. and B.S. = Scott's haematoxylin and Biebrich scarlet.
W.P. = Weigert-Pal's method.
R. = Ranson's method modified (8).

THE SUBCOMMISSURAL ORGAN

The subcommissural organ is hardly differentiated in the 16-mm. embryo, but is present in all the specimens from 25 mm. upwards. In the youngest embryo it appears as a specialisation of the ependymal cells in the mid-dorsal line immediately in relation with the posterior commissure. These cells differ from the rest of the ependyma in their greater length, their more deeply placed nuclei and their staining reactions. The lateral limits of the organ are sharply defined, but both cephalically and caudally the specialised cells gradually change into the ordinary ependymal cells. In the series examined well-developed, typical subcommissural organ cells are found extending from the site of the ventricular opening of the infrapineal recess down to the lowest limit of the posterior commissure. Cells of similar type but not so well defined line the floor of the infrapineal recess.

Near its upper limit the subcommissural organ occupies a relatively extensive region of the dorso-lateral ventricular wall, being limited ventrally by a groove (this groove is also described by Dendy and Nicholls (2)) (Plate I, fig. 1). Near the upper limits of the posterior commissure the subcommissural organ begins to recede from the lateral wall and to occupy a position only in the roof, but still limited laterally by the afore-mentioned grooves. The subcommissural organ lines the mesocoelic recess so that at the opening of the latter the organ once again occupies the dorso-lateral wall.

Dendy and Nicholls (2) describe the organ in a human foetus of 5 months as a bilateral structure "when traced backwards around the curve of the posterior commissure". In one only of our specimens (a 3-day infant) is this bilaterality seen, but in this specimen the double nature of the organ is very evident (Plate I, fig. 2).

Certain sections show well-marked fibre connections between the subcommissural organ and the ventral part of the posterior commissure: such connections have already been suggested by others (3).

THE MESOCOELIC RECESS

This recess in a 13-*week foetus* is wide and extends forwards for a short distance, its lining cells presenting the same characteristics as those of the subcommissural organ (Plate I, fig. 3).

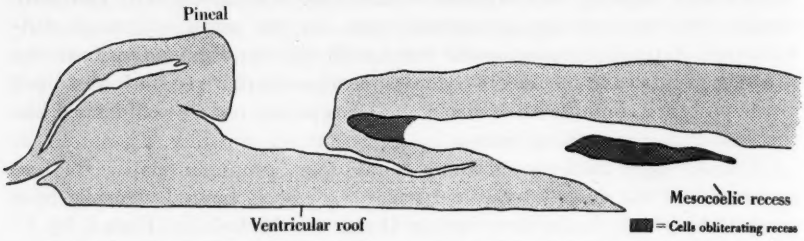
In the 15-*week foetus* the mesocoelic recess is large, but occlusion of its cephalic extremity by typical subcommissural organ cells has occurred, while caudally the closure of the recess is also beginning. This process of closure of the recess appears to be brought about in the region of its opening by the development of a shelf consisting of fibres and cells that grows across the recess from the sides, with the result that the original single opening becomes divided into two orifices leading from the recess into the ventricle (text-fig. 1).

In the 16-*week foetus* the actual opening into the ventricle is single, but the recess shows a small caudal diverticulum, possibly the remnant of the dorsal portion of the caudal part of the recess (text-fig. 2).

In the 18-*week foetus* the dorsal portion of the recess is partially occluded towards its cephalic end, but caudally it opens with the larger ventral part into the aqueduct.

Both the 36-*week and full-time foetuses* show a mesocoelic recess opening into the ventricle, but no caudal pocket or second opening.

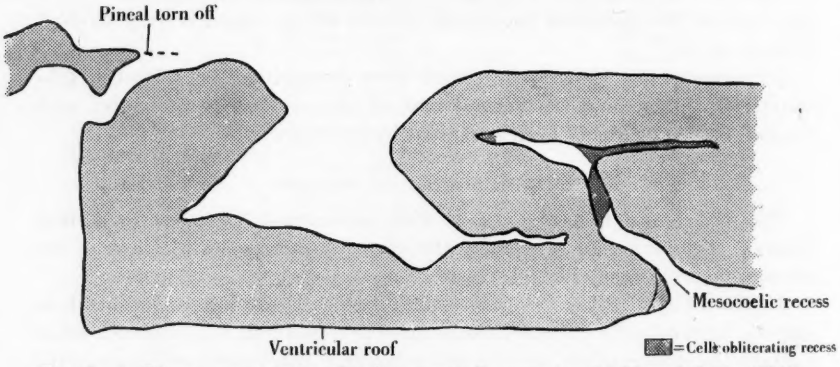
In the 3-*day infant* the recess is present: its main (ventral) part opens into the ventricle, but at its cephalic end it is occluded and the sections show that



Text-fig. 1. Linear reconstruction showing mesocoelic recess in a 15-week foetus (62). Approximate magnification: longitudinally × 133, vertically × 17.

this occluded portion once communicated with a closed tube lying dorsal to the main recess (text-fig. 3).

In the two 3-*month infants* (in one of which the sections were fully serial) no vesicle was found, but there were cellular remains of the mesocoelic recess skirted by the fibres of the posterior commissure (Plate I, fig. 4).

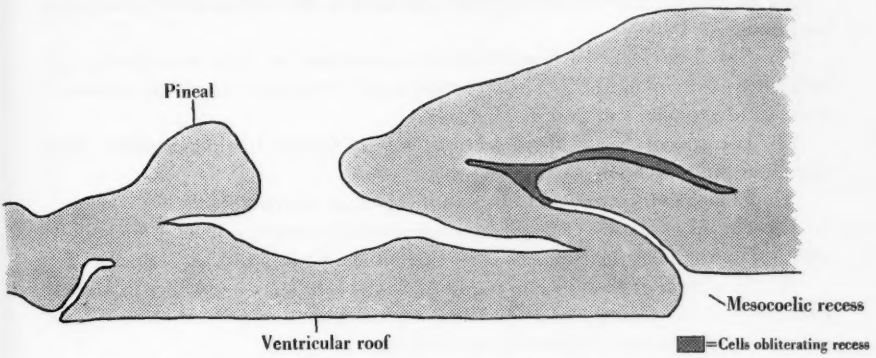


Text-fig. 2. Linear reconstruction showing mesocoelic recess in a 14–16-week foetus (1163). Approximate magnification: longitudinally × 137, vertically × 50.

The sections of the 6-*month infant* (not fully serial) showed a small vesicle representing the mesocoelic recess. In the 8-*month infant* scanty cellular remains only were found, and in the 9-*month* specimen both solid and small vesicular remnants were evident.

These observations show that the disappearance of the mesocoelic recess is gradual and variable, the process beginning between 13 and 15 weeks of foetal

development, the final closure being indefinitely delayed: Dendy and Nicholls (2) picture a lumen in the mesocoelic recess even in the human adult. These authors also describe the recess as curving back on itself in the 5-month human foetus. We, on the other hand, are inclined to think that the double orifice in text-fig. 1, the small caudal pouch in text-fig. 2, and the dorsal remnants of the pouch in text-fig. 3 may all be explained by an irregular process of occlusion of the originally large recess beginning probably in the region of the primitive opening. The occluding cells and fibres invade the recess from the lateral walls leaving for a time ventral and dorsal lumina, the latter becoming occluded before 26 foetal weeks, and the former at variable dates, if at all.



Text-fig. 3. Linear reconstruction showing mesocoelic recess in a 3-day infant (2338). Approximate magnification: longitudinally $\times 63$, vertically $\times 12$.

The cells lining the mesocoelic recess and also those throughout the floor of the infrapineal recess present the characteristics of the cells of the subcommissural organ (Plate II, fig. 1).

In the region of the opening of the mesocoelic recess into the aqueduct (i.e. very close to the caudal extremity of the subcommissural organ) the remains of the mesocoelic recess cells appear continuous with a fusiform, centrally placed plug of cells which occupies the midline of the central gray matter dorsal to the aqueduct (Plate II, fig. 2). This plug of cells extends throughout the midbrain, becoming more and more attenuated as it is traced caudally. The cells do not in this series appear to be differentiated from the surrounding cells, but are closely packed together. In the sections throughout the region of the junction of the ventricle and aqueduct there is a curious thinning of the ependymal cells covering the surface of this plug.

REISSNER'S FIBRE

The embryo, aged 15 weeks, in which this fibre was identified was put into 7 per cent. formalin within a couple of hours after abortion, and subsequently treated by a modification of Ranson's silver-pyridine method (8): the sections were cut serially and all were mounted.

The structure which we take to be Reissner's fibre (Plate II, fig. 3) appears in these sections as a sheet of degenerating tissue hanging into the ventricle from the subcommissural organ in the mid-dorsal line. This attachment extends from the opening of the infrapineal recess cephalically (Plate II, fig. 3) to the opening of the mesocoelic recess caudally (Plate II, fig. 4), and loose remnants are found continuing in the caudal direction for a short distance.

The somewhat indefinite nature of the structure of this "fibre" as seen in these sections caused us to weigh carefully the evidence for and against the possibility of its being Reissner's fibre.

The evidence *against* may be summarised as follows:

(1) Reissner's fibre has never been described in the human embryo as far as we know.

(2) A well-developed Reissner's fibre as described in other vertebrates is a long fibre made up of fibrils. The structure seen in this specimen is an extensive sheet of a reticular and granular nature.

(3) The appearance in these sections is very similar to that of débris that elsewhere we take to be shed cilia.

The evidence *in favour* may be summarised as follows:

(1) The specimen was fixed in an exceptionally fresh condition. Nicholls (1) states that the fibre degenerates with extraordinary rapidity after death.

(2) In certain of Nicholls' microphotographs (1) of Reissner's fibre in Fishes, the structure *is* extensive and sheet-like cephalically, and several of his figures are markedly similar to some of our sections.

(3) The cilia are apparently no more destroyed in the region where the "fibre" is found than in other parts. Furthermore, if the "fibre" seen in this specimen is only débris, it is strange that it should be massed in this place.

(4) The fact that this "fibre" is found in connection with the subcommissural organ is strong evidence in favour of its identity as Reissner's fibre.

(5) As the subcommissural organ is a degenerating structure in the human, Reissner's fibre may well show this granular and indefinite character.

SUMMARY

1. The subcommissural organ and the mesocoelic recess are described in the human as seen in twenty-eight specimens ranging from the 16-mm. embryo to the 9-month infant.

2. Reissner's fibre is described in a 15-week human foetus.

Our grateful thanks are due to all those who have so kindly supplied us with the material from which all these specimens are prepared. We also acknowledge our indebtedness to the University of London for the generous grants from the Thomas Smythe Hughes Medical Research Fund, without which it would have been impossible to collect so extensive a range of serial sections. Further we would record appreciation of Mr J. Anderson's Weigert-Pal preparations and of the microphotographs made by Mr A. V. Cobbett.

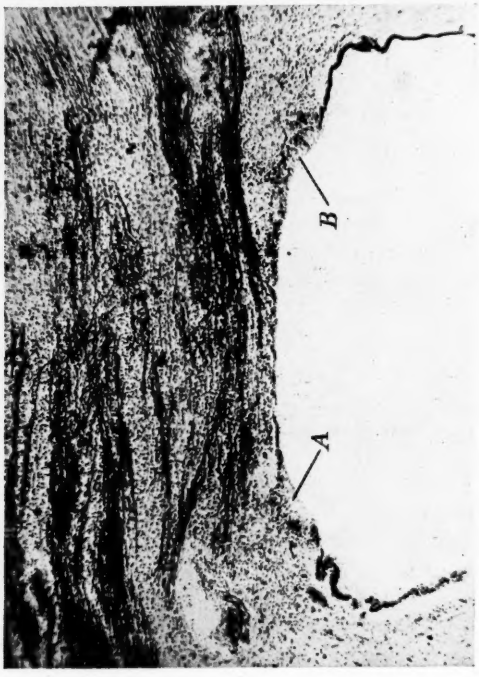


Fig. 2. Three-day infant. ×50. Bilateral subcommissural organ. *A*, right subcommissural organ; *B*, left subcommissural organ.

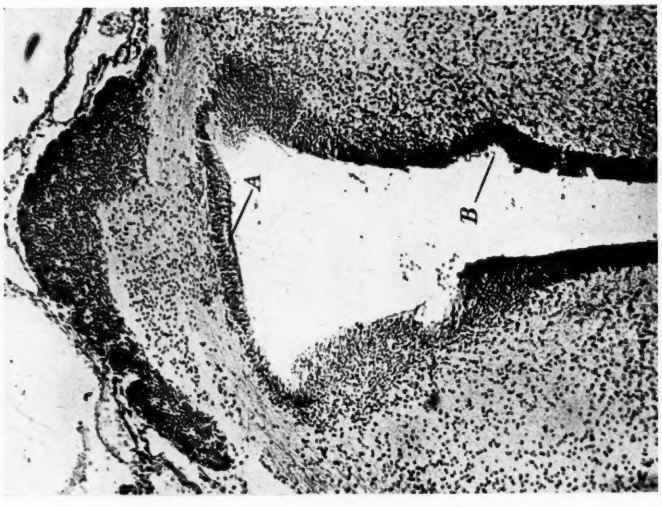


Fig. 1. Fifteen-week foetus. ×75. Subcommissural organ limited by grooves. *A*, subcommissural organ; *B*, groove.

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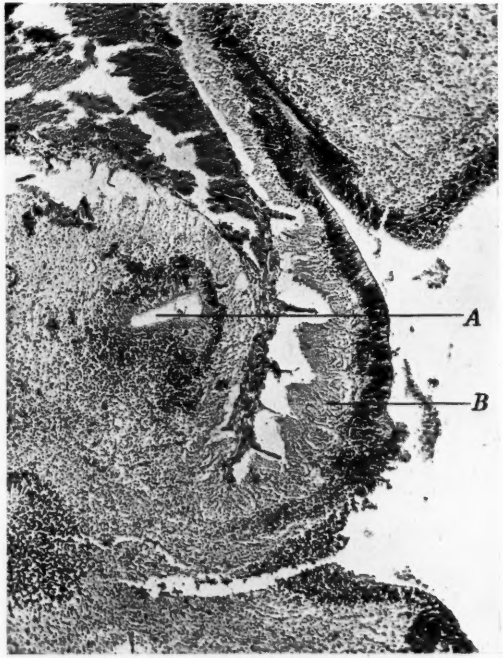

Fig. 3. Thirteen-week foetus. ×35. Sagittal section. *A*, mesocoelic recess; *B*, posterior commissure.

Fig. 4. Three-month infant. ×50. *A*, cellular remains of mesocoelic recess skirted by fibres of posterior commissure.

Plate I

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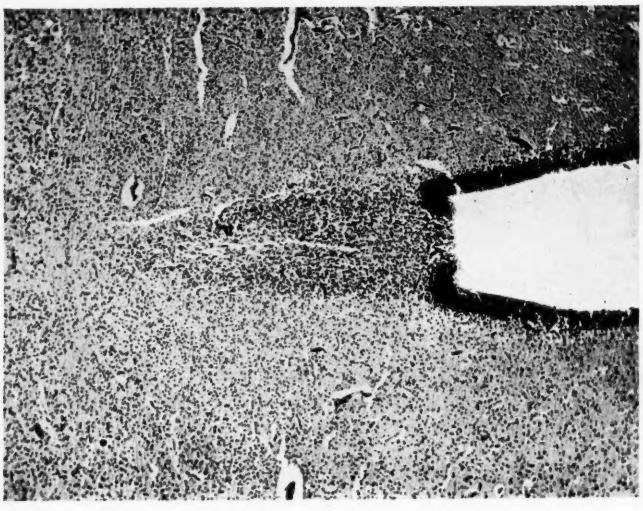

Fig. 2. Eighteen-week foetus. ×50. Plug of cells continuous with cells of mesocoelic recess.

Fig. 1. Three-month infant. ×12. Section shows cells in floor of recess similar to those of subcommissural organ. *A*, infrapineal recess; *B*, subcommissural organ in ventricular roof.

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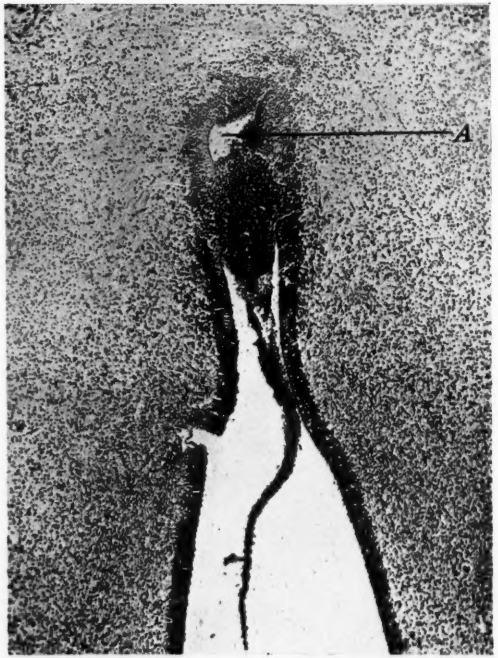

Fig. 3. Fifteen-week foetus. ×50. Reissner's fibre, cephalic extremity. *A*, infrapineal recess.

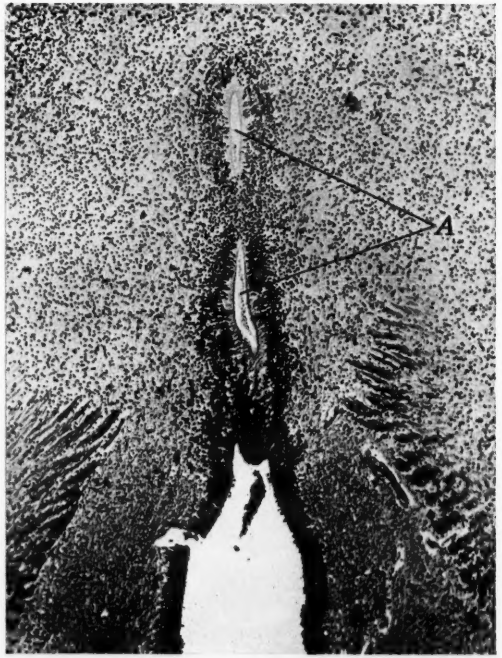

Fig. 4. Fifteen-week foetus. ×50. Reissner's fibre, caudal extremity. *A*, double opening of mesocoelic recess (see text-fig. 1).

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A PERONEUS TERTIUS MUSCLE IN A CHACMA BABOON (*PAPIO PORCARIUS*)

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INTRODUCTION

THE fact that a peroneus tertius muscle is present in certain apes has greatly modified previous conceptions based on the belief that this muscle was peculiar to Man. While it is true that the structure does not occur with the same constancy as in Man, it is by no means rare in the gorilla, as is revealed by the survey of Straus (1930). This author points out that M. peroneus tertius in the gorilla has been reported by Rothschuh in 1888, by Eisler in 1895, by Ranke in 1897, by Sommer in 1906 (this case is of doubtful nature) and by Morton in 1924 (two cases). In all the muscle was present in five or possibly six out of eighteen (i.e. approximately 30 per cent.) gorillas of which Straus was able to collect accurate data.

Hecker (1922) has reported a typical peroneus tertius muscle in a chimpanzee. No other record of its presence in this animal is mentioned by Straus or in other literature at my disposal. Straus, after citing these instances in gorilla and chimpanzee, continues: "This muscle does not occur in any other Primate. At least, I am unaware that a structure worthy of the name has been found. However, Forster (1916) describes a muscle M. extensor tarsi, which is inserted on the outer side of the calcaneus in a specimen of *Callithrix* (*Hapale*) *jacchus*. This muscle, despite its unusual insertion, is not probably homologous to the peroneus tertius of Man."

Like Straus, I have been unable to find in the literature any record of M. peroneus tertius in a lower Primate. The M. extensor tarsi described by Forster in the marmoset and cited by Straus, will be discussed in the body of this paper.

Recently, while dissecting the right foot of a young Chacma baboon (*Papio porcarius*), I observed an anomalous muscle, part of which is identical in character with the M. peroneus tertius as found in Man, gorilla and chimpanzee. The purpose of this report is to describe and briefly to discuss the significance of this specimen.

DESCRIPTION OF SPECIMEN

Fig. 1 is a dorso-lateral view of the dissection. To assist in the elucidation of the complicated arrangements revealed, fig. 2 A and B has been prepared. The former represents diagrammatically the normal distribution of the long

extensor tendons on the dorsum of the baboon foot. In the latter the additional structures found in this specimen are introduced.

The mutual relations of the muscles of the anterior compartment of the leg are essentially the same in the baboon as in Man. After passing beneath the

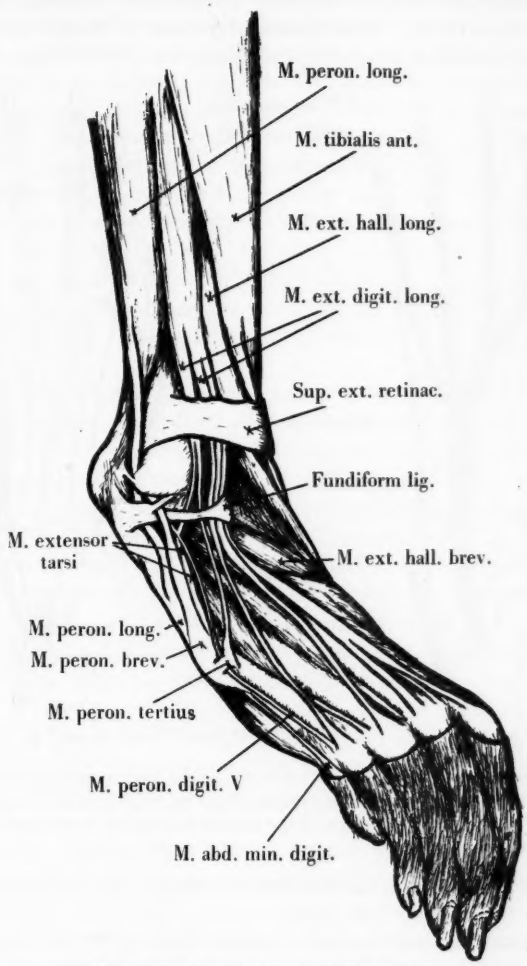

Fig. 1. Dorso-lateral view of the dissected foot.

superior extensor retinaculum (transverse ligament) the M. tibialis anterior forms two tendons which proceed towards the medial side of the foot. They are accompanied by the tendon of the M. extensor hallucis longus. The M. extensor digitorum longus mass is drawn towards the lateral side of the foot by a strong

fibrous sling arising from the dorsum of the calcaneus. This sling in the baboon is sharply distinguished from the deep fascia. None the less it is clear that this is the same structure which Retzius termed the *fundiform ligament* in Man. In Man, however, it is reinforced by bands derived from the deep fascia, the whole complex forming the inferior extensor retinaculum (cruciate ligament) as described by Bryce (1923). In the baboon I propose to denote this structure by Retzius' term fundiform ligament. The transformation of these ligamentous

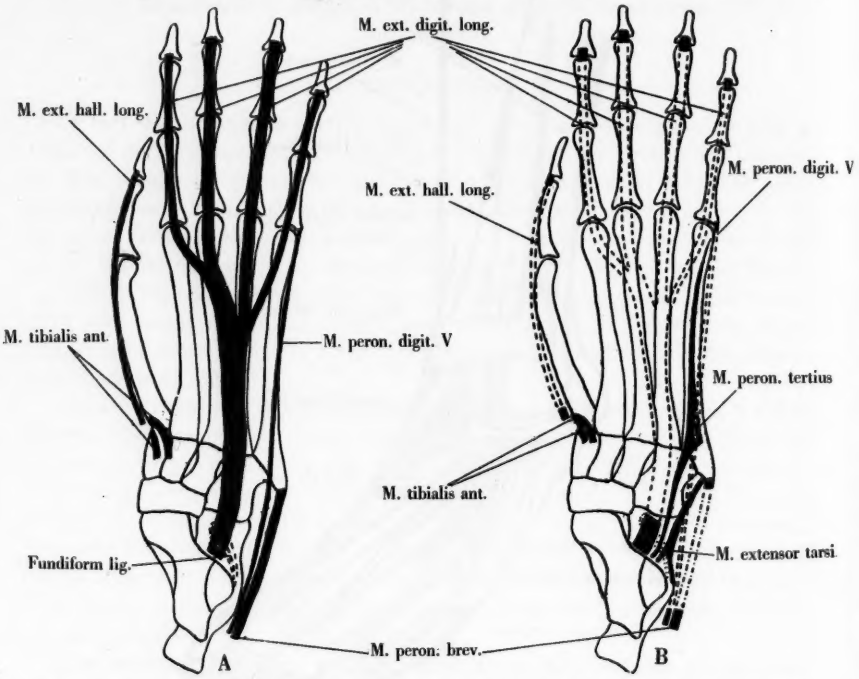

Fig. 2. A. Diagram showing the normal distribution of the long tendons on the dorsum of the baboon foot. B. Diagram showing the disposition of the tendons in the anomalous foot; the abnormal tendons in solid black. (In B the fundiform ligament is indicated by dotted lines but not labelled.)

slings and fascial bands through the primate series is itself a fascinating study, but is outside the scope of this paper.

In the normal baboon foot the muscular belly of M. extensor digitorum longus is undivided and forms a flat tendon which divides into three main fascicles. The distribution of these is shown in fig. 2 A. The medial fascicle, which is the largest, bifurcates to form a slender tendon to toe II and a much larger one to toe III. The intermediate fascicle, almost as large, proceeds to toe IV, and the slender lateral fascicle to toe V. Fig. 2 A also shows the long slender tendon of M. peroneus digiti quinti, which crosses the dorsum of the base of the

fifth metatarsal on its way to be inserted into the base of the proximal phalanx of toe V.

The anomaly found in the specimen now to be described involves the M. extensor digitorum longus. The belly of this muscle is divided in its distal portion into a larger medial and a smaller lateral portion. This division is visible in fig. 1. The medial portion furnishes the extensor tendons to the digits, whose distribution, represented by interrupted lines in fig. 2 B, is identical with the normal arrangement shown in fig. 2 A. The lateral portion gives rise to two slender tendons which are not represented in the normal baboon foot.

The more medial of these tendons runs distally and laterally to be inserted primarily into the dorsum of the base of the fifth metatarsal, and by a thin fascial expansion along the whole length of the shaft of that bone. At its insertion into the base of the metatarsal the tendon is perforated by that of M. peroneus digiti quinti.

This division of the M. extensor digitorum longus mass is thus practically identical in its origin, course and insertion with the M. peroneus tertius of Man, gorilla and chimpanzee. It satisfies all the criteria of a genuine M. peroneus tertius.

The more lateral tendon from the abnormal belly of the muscle diverges rapidly towards the lateral border of the foot. After passing through the aperture in the fundiform ligament, it expands into a broad triangular aponeurosis lying in the proximo-distal plane. The proximal portion of this aponeurosis is inserted into the antero-lateral portion of the superior surface of the calcaneus. Its point of attachment is just anterior and lateral to that of the fundiform ligament (fig. 2 B). The distal extremity of the aponeurosis gains insertion, in common with the tendon of M. peroneus brevis, into the tubercle of the fifth metatarsal. The intermediate portion of the aponeurosis has no attachment to bone. It forms a free edge lying in close relation with the tendon of M. peroneus brevis, but not attached to that tendon or to its sheath.

In so far as it has an insertion into the dorso-lateral aspect of the calcaneus, this derivative of the long extensor mass is comparable with the M. extensor tarsi of the marmoset as described by Forster. However, he does not indicate that there was any extension of the tendon to the base of the fifth metatarsal in the marmoset. Despite this, I believe that it is correct to homologise this derivative of the extensor mass in this baboon with that in the marmoset. I therefore designate this structure M. extensor tarsi.

The remaining muscles of this foot reveal no departure from the condition normal in the baboon. The other foot of this specimen has no trace of this or any other anomaly. Four other pairs of feet of *Papio porcarius* have been dissected and recorded in this Department. In none of them has this anomaly of the long extensor mass been noted. The incidence of the condition is therefore unilateral in one out of five individuals.

DISCUSSION

In this baboon there is present a structure which represents both the M. peroneus tertius of Man and the large anthropoid apes and the M. extensor tarsi of the marmoset. It is clear, therefore, that, though these two muscles cannot be regarded as completely homologous, Forster was right in postulating a very close relationship between them.

The insertions of the two divisions of the muscle are practically continuous with one another, forming an aponeurotic sheet extending along the outer side of the foot from the calcaneus to the head of the fifth metatarsal. In fact, the M. peroneus tertius and M. extensor tarsi may be regarded as being differentiated from a continuous fascio-aponeurotic sheet extending along the outer side of the foot.

This arrangement presents a close parallel to that existing on the medial side of the human foot. Hallisy (1930) has indicated "the association of M. tibialis anterior and M. extensor hallucis longus in a single musculo-aponeurotic sheet, more or less perfectly subdivided into two or more elements and inserted into the entire length of the inner margin of the foot from tubercle of navicular to distal phalanx". On the outer side of the foot it may now be postulated that there is a corresponding sheet extending from the anterior process of the calcaneus to the fifth toe, from which the peroneus tertius and extensor tarsi muscles are differentiated, although in the baboon this sheet could not be traced beyond the head of the fifth metatarsal. A tendon derived from M. peroneus tertius and joining the extensor expansion over the fifth toe is, however, well known. It has been observed in the chimpanzee by Hecker, in the gorilla by Morton, and in Man by numerous authors. This tendon may be regarded as differentiated in the anterior margin of the fascio-aponeurotic sheet.

In a previous paper (Wells, 1931) I have shown that the influence of terrestrial locomotion on the baboon foot has produced none of the architectural peculiarities shown by the human foot. These peculiarities of the human foot are due to its evolution through an intermediate stage represented by those of arboreal anthropoid apes, e.g. the gibbon. Consequently they are foreshadowed in the foot of the terrestrial gorilla. One of these peculiarities is the lateral longitudinal arch, for which the M. peroneus tertius is a support. The baboon foot is, however, wholly different in its mechanism, converging towards that of the Carnivore. It has no lateral arch mechanism, and no need for a specific supporting muscle for the outer side of the foot. The factors which might produce a differentiation *ad hoc* of the M. peroneus tertius in Man and gorilla are thus lacking in the baboon.

In the same paper I advanced the view that "in respect of the muscular system of the foot the ancestors of Man were more closely similar to the existing baboons than to the existing anthropoid apes". In arriving at this conclusion, the outstanding difficulty was that there was no evidence of a precursor of the peroneus tertius mechanism in the baboon foot. I was compelled at that stage to assume either that the ancestral type had possessed such

a precursor, which was not represented in the modern baboon, or that the M. peroneus tertius had been differentiated to meet the special mechanical needs of the human and gorilla foot.

From the specimen described in this paper, one of two inferences must be drawn. Either the ancestral type of baboon foot possessed the precursor of the peroneus tertius mechanism in a more or less differentiated form, or else there was inherent in it the potentiality to develop such a mechanism. The same inferences are to be drawn in the case of the ancestors of the human and gorilla foot. Either of these interpretations accords well with my former speculation that the muscular mechanism of the foot in baboon, Man and gorilla has arisen from a single type, and that the ancestral form has been least modified in the baboon, and most in the gorilla. At the least it may be said, adopting the conception so ably put forward by Le Gros Clark (1934), that in the three Catarrhine groups, of which the baboon, gorilla and Man are the most specialised representatives, there is the common potentiality to develop a peroneus tertius mechanism.

We may now go further. The arrangement described in the baboon demonstrates the common origin of the M. peroneus tertius of Man and the great anthropoid apes and the M. extensor tarsi of the marmoset. The divergent specialisation of this mechanism in the human and anthropomorph feet on the one hand, and in that of the marmoset on the other, may be correlated with differences of function. In both of these groups the foot mechanism as a whole may be regarded as highly specialised, while that of the Cynomorphs retains a much more generalised character.

Considered as isolated facts, these considerations would be of small significance. They assume a new importance, however, when it is observed that they accord exactly with a widely held conception of primate relationships.

The three Catarrhine groups, Cynomorph, Anthropomorph and human, are supposed to have a close ancestral relationship; it has now been demonstrated that *in all these groups the M. peroneus tertius may be developed, and this not wholly in response to merely functional needs.* The Platyrrhine group is held to be diversely specialised, but yet to stand closer to the Catarrhines than to other divisions of the Primates. In this group the M. peroneus tertius is not developed, but one of its members, the marmoset, shows the closely related M. extensor tarsi, which is also present in a more generalised form in the baboon, a representative of the Cynomorph group of Catarrhines.

Finally, the evidence presented in this paper of the simultaneous presence in a baboon of M. peroneus tertius and M. extensor tarsi, supports the view that the baboon and the Cynomorphs, though in certain respects specialised, are in others, including the mechanism of the foot, nearer to the generalised primate type than either the Anthropomorphs or the Platyrrhines.

CONCLUSIONS

1. An anomalous derivative of M. extensor digitorum longus has been observed unilaterally in one of five Chacma baboons. The aberrant portion of the muscle furnished two tendons. One of these, inserting into the base and shaft of the fifth metatarsal, is identical with the M. peroneus tertius of Man and certain anthropoid apes. The other, inserting into the dorsum of the calcaneus and the tubercle of the fifth metatarsal, has been identified with the M. extensor tarsi described by Forster in the marmoset.

2. This specimen demonstrates that the M. peroneus tertius and M. extensor tarsi are intimately related. These muscles are differentiated from a fascio-aponeurotic sheet extending along the outer border of the foot from the anterior process of the calcaneus to the fifth toe.

3. Reason is shown for believing that the appearance of M. peroneus tertius in the baboon is not to be attributed to the terrestrial habits of this animal. It is inferred that it is evidence either of a muscular mechanism possessed by the common ancestor of the baboon, chimpanzee, gorilla and Man, or of a common potentiality to develop such a mechanism.

4. The facts reviewed in this paper are in accordance with the view that the Catarrhines, whether Cynomorph, Anthropomorph, or human, have a close ancestral relationship, and that the Platyrrhines though divergently specialised are more nearly related to the Catarrhines than to other Primate groups. They further support the suggestion previously offered that in certain respects the Cynomorphs are the most generalised of all these Primates.

My thanks are due to Prof. R. A. Dart for allowing me to prepare this report, and for his valuable advice and criticism. I am also indebted to Dr A. Galloway and to Miss Margaret Orford for their interest and helpful suggestions, and to Mr G. W. H. Schepers for the preparation of fig. 1.

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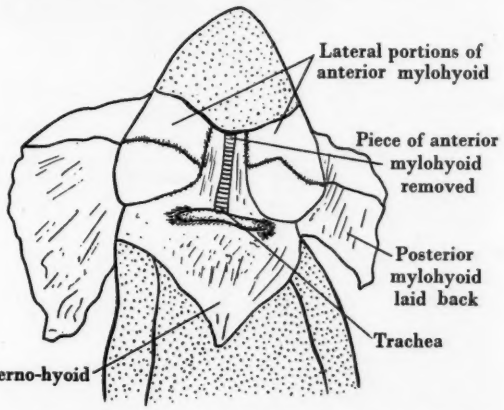
AN UNUSUAL THYROID GLAND IN A RACE OF LIZARDS (*EGERNIA KINGII*) FROM ECLIPSE ISLAND, WESTERN AUSTRALIA[1]

By GEOFFREY BOURNE, D.Sc.

The thyroid gland in members of the Reptilia varies somewhat according to the subclass.

In the Ophidia and in the Chelonia the thyroid is stated by Swale Vincent and Owen to be an unpaired body lying close to what Owen calls "the fork made by the divergence of the large and small carotids".



Text-fig. 1. Superficial dissection of the thyroid gland in *Egernia kingii*. A piece of anterior mylohyoid muscle is removed from the mid line. Posterior mylohyoid muscles laid back.

In the Lacertilia the thyroid, according to Swale Vincent, is bilobed in the younger forms and paired in the older ones and lies just in front of the pericardium. Owen states that the thyroid in lizards is frequently single and is usually broader than it is long. He found it double in the monitor, single in geckos, scincs and chameleons, and found it overlapped by the pharyngeal pouch in the latter.

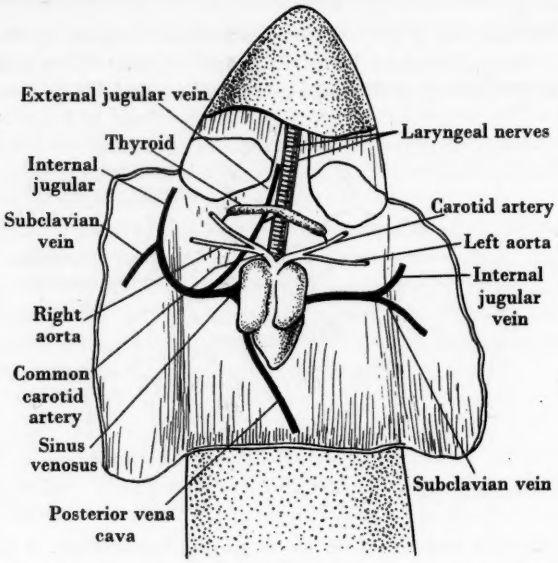
In *Egernia kingii* from Eclipse Island, Western Australia, the thyroid differs from any previously known thyroid gland in any class of Vertebrates (text-fig. 1).

The gland was found to be an elongated, rod-shaped structure orientated transversely across the throat and possessing but slight attachment to the surrounding tissue.

[1] Portion of this work was carried out while working under a Hackett Research Studentship of the University of Western Australia.

If the posterior mylohyoid muscles are laid back and a section of the sterno-hyoid removed, the thyroid may be seen as an apparently cartilaginous bar extending transversely across the trachea, portion of which is also exposed. In this situation the gland looks remarkably like a portion of the hyoid apparatus, and in fact this was at first thought to be the case, particularly as its frosted glass appearance was suggestive of cartilage.

Dissection of the remainder of the sterno-hyoid muscle and separation of the pectoral girdle brought the vascular relationships of the thyroid into view. These are represented diagrammatically in text-fig. 2.



Text-fig. 2. Anatomy of the thyroid gland in *Egernia kingii*. Sterno-hyoid and mylohyoid muscles removed.

From the sinus venosus arising from the right auricle were given off as usual a subclavian vein and a posterior vena cava. From the subclavian, near its point of origin, was given off an external jugular vein which passed across to the trachea and ran alongside it near the floor of the mouth. It gave off a large and well-defined branch to the centre of the thyroid. As in other lizards, there was no left external jugular vein.

From the ventricle were given off two pairs of vessels, the right and left aortae and common carotids.

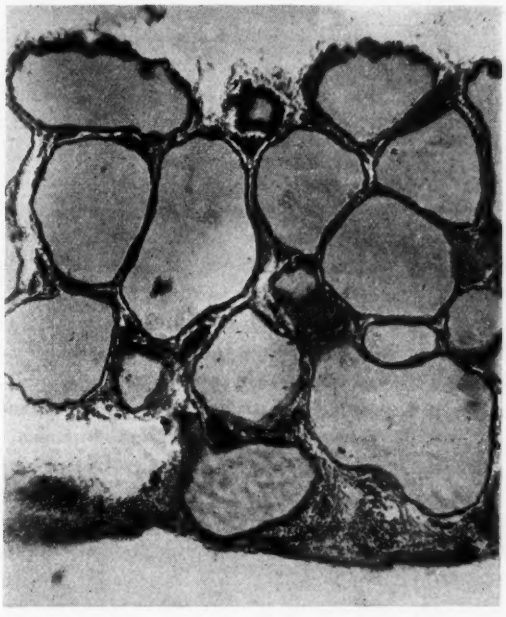
From each of the carotids a fine branch, imbedded in connective tissue, was given off to either end of the thyroid. The direction of the flow of the blood in this case then is from either end to the centre and out from the centre into the external jugular vein.

The nerve supply was found to take the form of two fine branches from the laryngeal nerves of either side.

MICROSCOPIC STRUCTURE OF THE THYROID

On sectioning it was found that the whole length of the bar was made up of vesicles filled with a structureless colloidal material (text-fig. 3).

In some of the thyroids examined the gland was found to be covered in parts by a thick rather cellular capsule, in other specimens the capsule was



Text-fig. 3. Longitudinal section through the thyroid gland of *Egernia kingii*.

practically absent and the follicular lining was in contact with the surrounding tissue.

The size of the follicles varied considerably, but most of them were large. The smallest follicle measured approximately 0·03 mm. and the largest approximately 0·24 mm., and they were very closely packed together.

A mass of connective tissue was found near the heart, but microscopical examination of this revealed the presence of neither thymus, parathyroid nor further thyroid tissue. No parathyroid tissue could be observed in association with the thyroid itself.

There was practically no interfollicular epithelium in the thyroid, but there were a large number of blood and lymph spaces between the follicles (Plate I, fig. 1).

Some of the follicles were imperfectly subdivided by septa. The follicles were connected by a few strands of fibrous tissue and a few of these fine fibres also surrounded the follicles in some places (Plate I, fig. 2).

Every follicle was filled to its capacity with colloidal material, so much so that the cells were squashed quite flat, even the nuclei being unrecognisably distorted. So great was this distortion that in every case the epithelium appeared as an endothelium, and this, together with a few fibres associated with the flattened cells, gave the appearance of a follicle surrounded only by connective tissue, a true follicular epithelium appearing absent (Plate I, fig. 2).

In no cases were cuboidal cells observed, and the cells present could not be differentiated into the chief cells and colloid cells of Langendorff. They all belonged to that type known as chief cells, since they possessed a pink staining cytoplasm with vesicular nuclei.

The chief cells are believed to be the inactive stage of the thyroid gland, and the fact that the cells of this gland resemble chief cells in their staining reaction and are so completely flattened, while the follicles are packed with colloid, indicates that these cells are at the extreme of inactivity. It is curious that every lizard examined from Eclipse Island showed a similar type of thyroid. It is an important fact, however, that all these lizards were collected at the same time of the year, that is, towards the end of the winter months, during which time the thyroid was apparently not much in demand. There was no doubt that the gland contained an extraordinary load of colloid, every follicle being packed to capacity and its lining epithelium squashed quite flat. No trace of lymphoid tissue could be found in the gland.

Cramer had previously stated that the flattened cells and accumulation of colloid meant inactivity of the gland. He found the epithelium of the thyroid gland of mice fed on dried thyroid for three months to be completely flattened and in some cases to be atrophied.

Krause states that the pressure of contained colloid in the cells tended to flatten the epithelium, and this is probably the cause of the abnormal flattening in the *Egernia* thyroid. Both Bremer and Cooper state that the epithelium of the thyroid flattens in old age, but this is not a likely explanation in this case.

The present author has found the epithelial cells of the Wallaby thyroid to be of a low cuboidal nature, although the follicles were filled with colloid. It is assumed that in the case of *Egernia* the follicles were under a state of much greater tension.

It is of interest also that the intervesicular tissue of the *Egernia* thyroid is entirely fibrous in nature, this being a point of similarity with the frog thyroid (Swale Vincent).

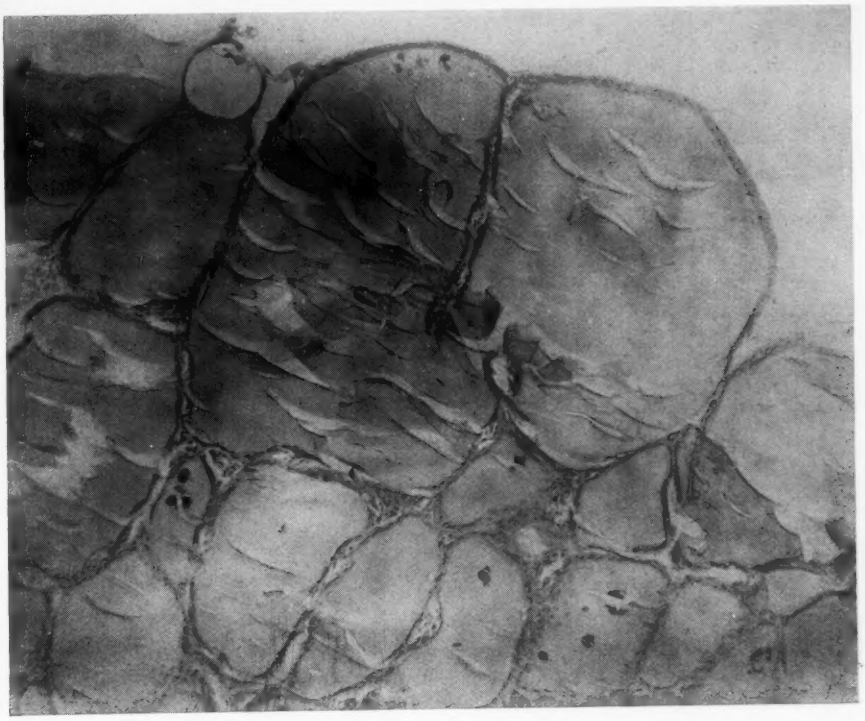


Fig. 1.

Fig. 2.

UNIV. OF MICH.

CONCLUSION

In this paper a short account has been given of the anatomical position and microscopical structure of the thyroid gland in the lizard *Egernia kingii*. It has been found to consist of a cartilaginous looking bar stretched across the trachea and composed of thyroid follicles filled with colloid apparently under a high state of tension, since the epithelial cells of the follicles were squashed out of recognition.

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EXPLANATION OF PLATE I

Fig. 1. Follicle (bottom) abutting on blood capillary (top). A red blood corpuscle may be seen adhering to the wall of the capillary and other blood cells may be seen towards its centre. On the bottom wall of the capillary may be seen the nucleus of an endothelial cell, and just below it two nuclei belonging to follicular cells showing signs of distortion. The follicle is filled with a colloidal material.

Fig. 2. Showing various sized follicles and partial separation of the large follicle into two parts by a growth of septum. Dark spots of mucus may be seen lying among the colloid in many follicles.

THE CORONARY BLOOD SUPPLY IN THE *RHESUS* MONKEY

By DAVID I. ABRAMSON and HAROLD J. EISENBERG

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This report is concerned with a description of the coronary blood supply in the *rhesus* monkey as revealed by injection of the blood vessels.

Sixty hearts, taken from animals of varying ages, were used. The coronary arteries were filled with an injection mass consisting of a suspension of either an oil paint in acetone or of finely pulverised coloured chalk in water. The hearts were gradually dehydrated in alcohol and then cleared in methyl salicylate.

RIGHT CORONARY ARTERY

The right coronary artery arises from the aorta at the level of the free edge of the right anterior semi-lunar cusp. It enters the auriculo-ventricular groove as the right circumflex artery, and proceeds to the right over the anterior surface of the heart (fig. 1, *A*). In its course it gives off from one to three large branches and a variable number of small ones, all of which extend downward over the anterior surface of the right ventricle. The right circumflex artery, continuing in the auriculo-ventricular groove, winds around the margo acutus (lateral border of the right ventricle) at which point one large branch, or less frequently a number of small vessels, arise. These reach the extreme tip of the right ventricle, in many cases to supply its lateral aspect. The above subdivisions, as well as those springing from the right circumflex artery in its anterior course, give off fine twigs to either side as they descend in the direction of the apex.

Posteriorly the right circumflex artery remains in the auriculo-ventricular groove for variable distances. In about 28 per cent. of cases (seventeen hearts) it extends as far as the crux. Here it turns abruptly to run in the posterior interventricular sulcus as the posterior descending artery, dividing into its sub-branches at a point one-half to two-thirds the distance from base to apex (fig. 4, *B* and *C*). In the above series, the right circumflex artery in its posterior course gives off a variable number of small vessels which descend for a short distance in the direction of the apex. From the terminal portion of the right circumflex artery (posterior descending artery), five to seven branches arise, all of which run across the right ventricle in the direction of the margo acutus. Other vessels are also given off from the posterior descending artery, some of

which are distributed to the left for a short distance while others penetrate the septum perpendicularly. In the remaining 72 per cent. of cases (forty-three hearts), the right circumflex artery, instead of reaching the crux, gradually terminates by dividing into small branches which run for short distances over the basal portion of the posterior surface of the right ventricle.

LEFT CORONARY ARTERY

The left coronary artery arises from the aorta at the level of the free edge of the left anterior semi-lunar cusp. It turns to the left to run in the auriculo-ventricular groove for about 3 mm. and then divides into its two main branches, the anterior descending and left circumflex arteries (fig. 2).

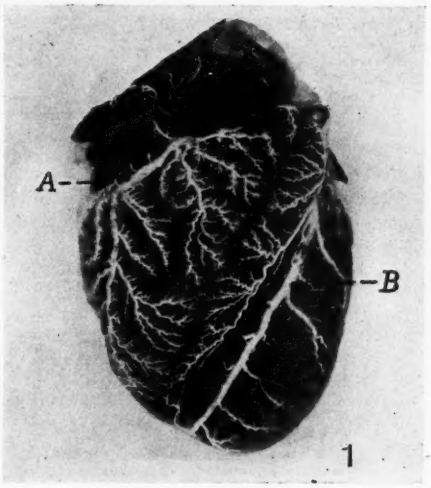


Fig. 1. Anterior surface of the heart. *A*. Right circumflex artery in the auriculo-ventricular groove, giving off perpendicular branches which course in the direction of the apex. *B*. Anterior descending division of the left coronary artery, in the anterior interventricular groove. Arising from it are seen vessels which extend to the right, to the left, and perpendicularly into the septum.

ANTERIOR DESCENDING ARTERY

At its origin, the anterior descending artery leaves the auriculo-ventricular groove to course down the anterior interventricular sulcus to the apex (fig. 1, *B*). At this point, in a great majority of cases, it divides fan-like into two or three terminal branches, one of which continues inferiorly and then around the apex posteriorly to run basalward for a short distance in the posterior interventricular sulcus (fig. 3, *E*). The remaining one or two subdivisions are distributed either to the right or to the left on to the posterior surface of the heart. In a small number of cases, the anterior descending artery, itself, turns

around the apex to ascend the posterior interventricular sulcus for almost one-third the distance from apex to base, and then divides into two or three branches.

During its course, the anterior descending artery gives off vessels to the right, to the left, and from its under surface, the latter penetrating the septum perpendicularly. The branches arising from the right side of the anterior descending artery vary in number, either from one to three large vessels or from three to seven small ones. These, or their fine ramifications, usually extend as far as the junction of the septum and the adjoining portion of the right ventricle, giving off twigs to either side in their course (fig. 1). From the left side of the anterior descending artery, three to six vessels of variable size arise, all of which are distributed on to the anterior aspect of the outer wall of the left

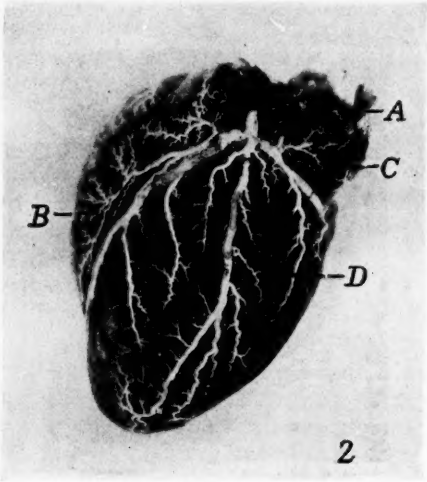


Fig. 2. Outer wall of the left ventricle with margo obtusus in the foreground. *A*. Left coronary artery. *B*. Anterior descending division in anterior interventricular groove. *C*. Left circumflex division in the auriculo-ventricular groove. *D*. Branch arising at the bifurcation of the left coronary artery which descends the margo obtusus.

ventricle. Some of these run horizontally to the obtuse border of the heart, while others descend obliquely in the direction of the apex. From these, in turn, arise numerous fine vessels which spread over the anterior and lateral aspects of the outer wall of the left ventricle (fig. 2).

LEFT CIRCUMFLEX ARTERY

The left circumflex artery from its origin proceeds in the auriculo-ventricular groove to the left, extending over the anterior surface of the left ventricle and around the margo obtusus (lateral border of the left ventricle) (fig. 2, *C*). In more than half of the cases, a large branch is found arising either from the left

coronary artery at its bifurcation, or from the left circumflex division near its origin (fig. 2, *D*). This branch generally runs obliquely to the left as far as the obtuse border, over which it extends in the direction of the apex for a variable distance. During its course it gives off vessels to either side, some of which extend on to the anterior aspect of the outer wall of the left ventricle, while others reach the posterior surface. In its anterior and lateral course, the left circumflex artery gives off a few small perpendicular branches and occasionally a large one which are distributed to the basal portion of the left ventricle. Posteriorly, either one to three large branches or two to five small ones arise

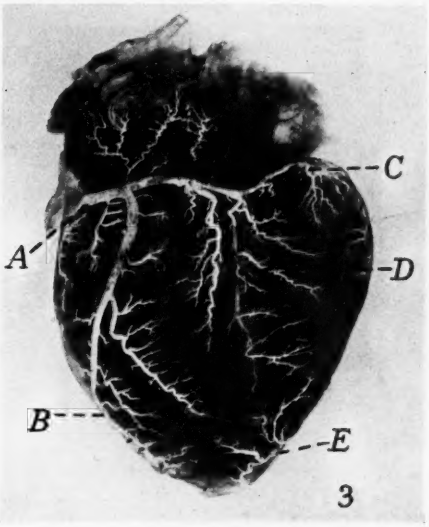


Fig. 3. Posterior surface of the heart (72 per cent. of cases). *A*. Left circumflex division in the auriculo-ventricular groove. *B*. Large branch of the left circumflex division extending on to the margo obtusus. *C*. Terminal branch of the left circumflex division in the auriculo-ventricular groove, extending as far as the lateral border of the right ventricle. *D*. Posterior descending artery, another terminal branch of left circumflex division, in posterior inter-ventricular groove. *E*. Arborisations of the anterior descending artery on the posterior surface of the apex.

from the left circumflex artery, all of which extend downward over the posterior surface of the left ventricle.

In 72 per cent. of cases (forty-three hearts), the left circumflex artery extends as far as the crux. At this point it either turns abruptly to descend in the posterior interventricular sulcus as the posterior descending artery, or it terminates as two branches, one of which follows a similar course in the posterior sulcus (fig. 3, *D*). In the latter hearts, the other terminal branch of the left circumflex artery usually continues in the auriculo-ventricular groove for a

short distance, giving off a few small twigs which are distributed to the basal posterior portion of the right ventricle (fig. 3, *C*). The posterior descending artery in the above series proceeds in the posterior interventricular sulcus in the direction of the apex for a variable distance, in a majority of cases terminating into two branches at a point about half the distance between base and apex. One of the terminal subdivisions of the posterior descending artery usually continues in the posterior interventricular sulcus, while the other extends to the right. From the latter branch and from the right side of the posterior descending artery, arise numerous small vessels which are distributed

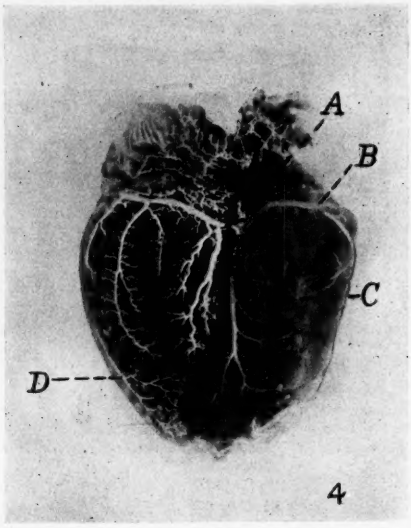


Fig. 4. Posterior surface of the heart (28 per cent. of cases). *A*. Left circumflex artery in the auriculo-ventricular groove, dividing into its terminal branches. *B*. Right circumflex artery in the auriculo-ventricular groove, extending as far as the crux. *C*. Posterior descending artery, a continuation of the right circumflex artery, in the posterior interventricular groove. *D*. A lateral branch of the left circumflex division, coursing down the margo obtusus.

to the right ventricle as far as the margo acutus (fig. 3). In its course, the posterior descending artery, as well as its terminal branch which continues in the groove, gives off a number of vessels, which supply either the adjoining portion of the left ventricle or penetrate the septum perpendicularly.

In the remaining 28 per cent. of cases (seventeen hearts), the left circumflex division leaves the auriculo-ventricular groove at some point to the left of the crux to divide into its terminal branches. One of these descends in the direction of the apex, usually in close proximity and parallel to the posterior interventricular sulcus (fig. 4).

SUMMARY

The coronary blood-vessel distribution in the *rhesus* monkey was investigated in sixty injected hearts.

The outer anterior and lateral walls of the right ventricle are generally supplied by the perpendicular branches of the right coronary artery. The anterior aspect of the septum, making up the part of the anterior surface of the heart intervening between right and left ventricles, receives its distribution from vessels arising from the right side of the anterior descending division of the left coronary artery. The outer wall of the left ventricle, on its anterior and lateral aspects, is supplied entirely by branches of the left coronary artery. Vessels which arise from the left side of the anterior descending division anastomose with one another and with twigs from the left circumflex division.

On the posterior surface of the heart, considerable dissimilarity in the distribution of the large blood vessels is found. In 72 per cent. of cases, all of the left ventricle and part of the right, ranging from a strip proximal to the interventricular sulcus to almost the whole of the posterior surface, are supplied by the left coronary artery. In this series, the upper two-thirds of the septum is supplied anteriorly by the penetrating branches of the anterior descending division, and posteriorly by similar twigs from the posterior descending artery (either a branch or the terminal portion of the left circumflex division). The apical portion of the septum, both anteriorly and posteriorly, receives its supply generally from penetrating branches of the anterior descending division. In the remaining 28 per cent. of cases, practically the whole of the right ventricle posteriorly (with the exception of its extreme tip) is supplied by branches of the right circumflex artery. The whole of the left ventricle posteriorly receives its supply from branches of the left circumflex division. In this series, the upper two-thirds of the septum receives its distribution anteriorly from penetrating branches of the anterior descending division of the left coronary artery, and posteriorly from twigs of the posterior descending division of the right circumflex artery. The apical portion is supplied by branches of the anterior descending artery.

We wish to thank the Infantile Paralysis Commission of the Long Island College of Medicine for their kindness and co-operation in supplying us with the hearts used in this study.

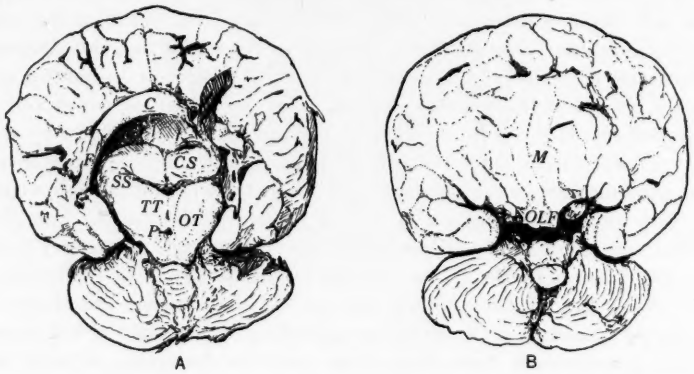
ANATOMICAL NOTES

A CURIOUS ABNORMAL HUMAN BRAIN

By J. E. FRAZER

No history or record accompanied this curious example of cerebral abnormality, which was found among some old stores of pathological material and bore the simple label "Porencephaly". The specimen has been cut and injured in various ways, and is not in the best condition, but appears to have come from a foetus at term, or perhaps from an infant after birth.

The brain stem seems to be normal, the diverging crura including corpora mamillaria (apparently normal) between them, while a somewhat flattened tuber lies between these and a normal chiasma: a perforation indicates the one-time position of the infundibulum. On the dorsal side the tectal structures are easily recognised above and in front of the vermis, while, in front of these, the optic thalami give the impression of being somewhat splayed out; but this may be an effect of the remarkable condition of the telencephalic formations which makes the interest of the specimen.



The abnormal portions of the brain are found, then, only in those parts which are developed from or in association with the cerebral vesicles. These two embryonic formations, instead of developing separately as "hemispheres", have grown in what appears to be a continuous mass in front: thus there is no falx cerebri, no separation at all in fact between them, and the brain is a single mass viewed from behind or from the front. Nevertheless the two vesicles have not had their potentialities of structural growth destroyed, or affected in any way, apparently, except mechanically, so that the main parts are easily recognised.

In the figure, A shows the specimen from behind, B from the front. The feeble line *M*, on the front surface, may indicate what ought to have been a separation between the two halves, but this is uncertain. This line passes below on to the middle of a bluntly pointed process (*OLF*) which represents, possibly, partly fused olfactory structures: the condition of the specimen keeps one from certainty in this matter. Further out on each side, however, there is no difficulty in recognising the temporal lobes, and in placing the Sylvian fissures. The gyri and sulci on the outer surfaces of these lobes can be made out more or less satisfactorily, but those above the line of the Sylvian fissure, and those in front, are much more doubtful.

Looked at from behind (A) there is a wide cavity, in which one can recognise the optic thalamus (*OT*) on each side, the two striate bodies (*CS*) in front of these, with the stria semicircularis (*SS*) and striate vein, while what is plainly the "roof of the lateral ventricle" rises up from in front of the corpora striata. A rounded fold (*C*) runs transversely above this, and suggests at first a possible representation of the corpus callosum: examination, however, shows that it is really made by the (somewhat thickened) roof plate, folded up here and hardened in position, while the structure against which it lies appears to be of the nature of a convolution. Laterally and further back, is a formation which probably represents the fornix (*F*).

There is no indication—beyond the strip of roof plate mentioned—of the roof of the third ventricle or of its continuity on to the cerebral region. Thus, although its attachments probably formed a broad T, there is no chance of verifying this on the specimen. Slight linear elevations (*TT*) run back, converging toward the habenular region, and seem to represent the taenia thalami on each side. It seems not improbable that the roof plate as a whole bulged dorsally to a large extent. The small perforation (*P*) visible between the hinder parts of the thalami was taken to represent the opening into the pineal recess (torn off) in which case the bridge of tissue in front of it would be the habenular commissure: still further forward the massa intermedia may be represented, and the deep pit in front of this leads down to the infundibular region.

If the opportunity serves, an examination in detail of the specimen will be made by sections: in the meantime it seems worth while to put the appearances on record briefly.

MACRODACTYLY, WITH REPORT OF A CASE

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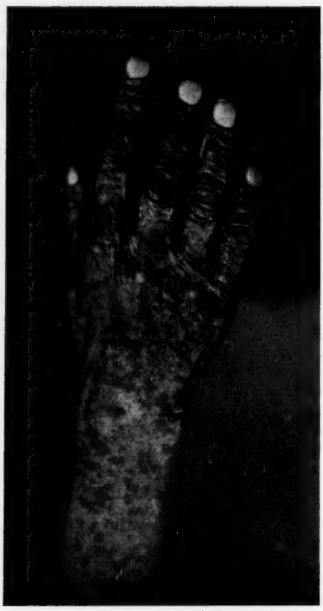
Assistant Medical Registrar, Middlesex Hospital

Of the various developmental defects of the fingers macrodactyly is one of the least common. About seventy-seven cases only are on record in comparison with many hundred cases of brachydactyly, syndactyly, supernumerary digits and arachnodactyly.

The aetiology of the condition remains uncertain. Against its being a purely genetic condition, i.e. due to some defect or abnormality of the germ plasm, have been



brought the following facts. In only one of the reported cases is there a family history of the condition; in almost every case it is unilateral, and only rarely is it associated with other congenital abnormalities. The other congenital abnormalities of the fingers which do give clear evidence of inheritance are usually bilateral and they are very frequently associated with other congenital defects. In a number of the cases the enlargement was due mainly to overgrowth of the soft tissue of a neurofibromatous or angiomatous nature, suggesting a relation to these conditions. Several of them were associated with overgrowth of other bones in the body, such as the maxillae, clavicle, zygoma, etc., suggesting that there may be some relation to lecntiasis ossea or multiple exostoses, or to some endocrine dysfunction. (Kanavel, 1932.)

The thumb, index and middle fingers are the digits most commonly affected, and it is usually limited to the three phalanges, the metacarpals being unaffected. X-ray examination may show some increase in the density of the bone cortex.

The illustration shows a case found in a middle-aged woman admitted to hospital suffering from acute yellow atrophy of the liver and exfoliative dermatitis from which she subsequently died. No family history of the condition could be traced, and there was no consanguinity. The condition was bilateral, both index fingers being identically affected. It had been present from birth and had never been the site of any disease or disability since. No other congenital abnormalities were found in the patient. The enlargement was almost entirely one of increase in length, this being due to an increase in size of the first phalanx, the metacarpal and other phalanges being normal in size, and the soft tissues appeared normal in every respect. At post-mortem examination the skin, apart from the condition of exfoliative dermatitis and the subcutaneous tissues, appeared normal. A microscopical examination was not made.

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SOME VARIATIONS IN THE MUSCULATURE OF THE SUPERIOR EXTREMITY

By N. PAN

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In a well-developed and muscular adult male subject, aged about 30, dissected in the Department of Anatomy of the Calcutta Medical College, certain variations in the muscles of the superior extremity were noticed, which, because of their rarity, I am reporting a description.

Pronator quadratus

This muscle consists of two portions, entirely separate in origin, course and insertion. The superficial portion is triangular in shape and takes origin by a tendinous pointed apex from the medial surface of the base of the ulnar styloid process. The muscle fibres radiating from this tendinous origin, in a fan-shaped manner, overlap the deep portion of the muscle and are inserted into a triangular area at the lateral part of the volar surface of the lower fourth of the radius (fig. 1). The deeper part is quadrilateral in shape, and arises from the lower fourth of the dorsal border and the adjoining medial and volar surfaces of the ulna by fleshy fibres. These fibres pass lateralwards, with slight obliquity downwards, and are inserted, (1) by an aproneurotic lamina into the medial part of the volar surface of the lower fourth of the radius, and (2) by fleshy fibres into the triangular rough area above the ulnar notch at the lower end of the radius (fig. 2), so that the triangular superficial part of the muscle overlaps the lower and lateral part of the deep portion of the muscle from which it is completely separated by an intermuscular interval. This duplicature of the pronator quadratus was found on both sides of the body. As regards the nerve supply, the volar interosseous branch of the median nerve passes underneath the deep portion as usual, and, after supplying it, sends twigs to the deep aspect of the superficial part for its supply.

In Morris's *Human Anatomy* (9th ed.) the following variations of the pronator quadratus muscle are noted: "It may be missing or may extend further up the forearm than usual or down upon the carpus. It may be triangular or divided into parts, the fibre bundles of which take different directions. It may send fasciculi to the carpus or metacarpus or be fused with the flexor carpi radialis brevis." This muscle therefore, as described above, is not included in the variations noted in Morris's book neither do the variations mentioned in Piersol's and Quain's *Anatomy* cover the description of the muscle noted here.

Subscapulo-humeralis

A thin muscle, quadrilateral in shape, $1\frac{1}{4}$ in. in breadth and 2 in. in length, is present in the left arm (fig. 3) crossing the tendon of the subscapularis vertically along its ventral aspect. Its oblique aponeurotic origin is from the ventral aspect of the tendon of the subscapularis extending higher medially towards the root of the coracoid process. Its tendinous insertion is chiefly into the crest of the lesser tubercle of the humerus just above the insertion of the teres major and slightly under cover of its tendon. In the right arm the muscle (fig. 4) is less wide ($\frac{1}{2}$ in.) but considerably thicker and is fusiform in shape. It is also shorter, being $1\frac{1}{2}$ in. in length. Its tendinous origin above is fused with the ventral aspect of the tendon of the subscapularis on a lower level than on the left side and much below the root of the coracoid process. Its insertion into the humerus is the same as on the left side. Filaments of the lower

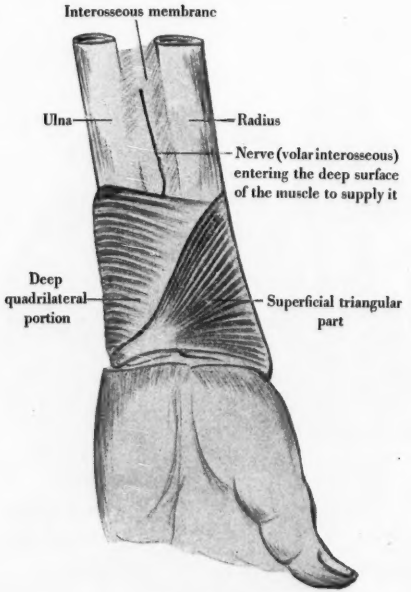
Interosseous membrane
Ulna
Radius
Nerve (volar interosseous) entering the deep surface of the muscle to supply it
Deep quadrilateral portion
Superficial triangular part

Fig. 1.

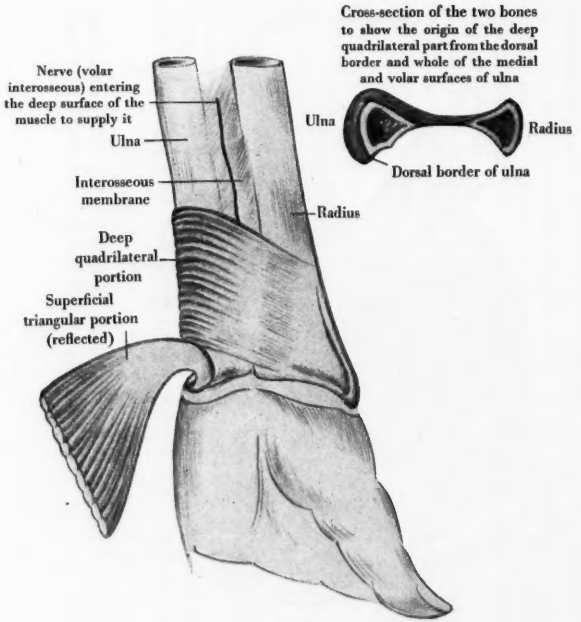
Cross-section of the two bones to show the origin of the deep quadrilateral part from the dorsal border and whole of the medial and volar surfaces of ulna
Ulna
Radius
Dorsal border of ulna
Nerve (volar interosseous) entering the deep surface of the muscle to supply it
Ulna
Interosseous membrane
Radius
Deep quadrilateral portion
Superficial triangular portion (reflected)

Fig. 2.

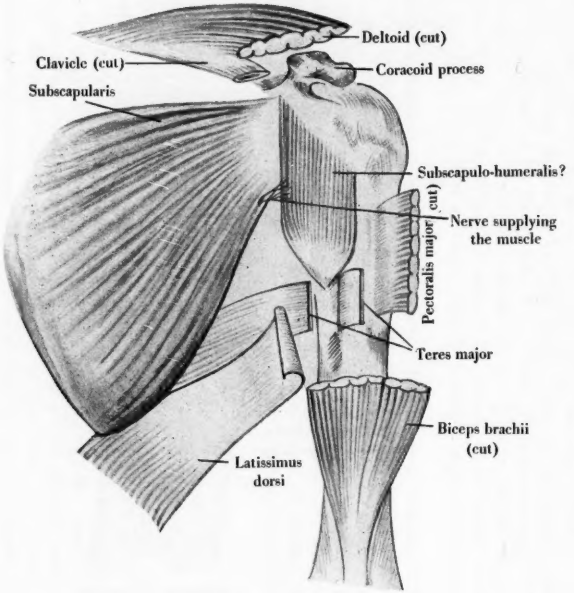

Fig. 3. Left side.

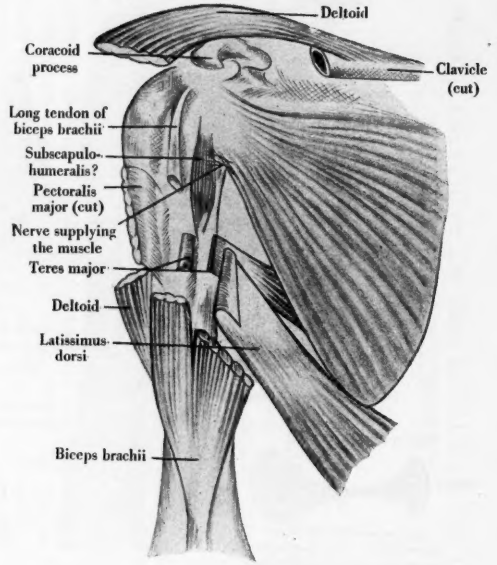

Fig. 4. Right side.

subscapular nerve enter the medial border of the muscle along the lower part of the subscapularis near its tendinous termination.

This peculiar muscle is not mentioned amongst any of the variations noted in connection with the neighbouring muscles. It is not the deep superior portion of the coraco-brachialis which arises from the coracoid process and is supplied by the musculo-cutaneous nerve. It may be named "subscapulo-humeralis" in consideration of its origin and insertion.

Associated with these variations in the same superior extremity is found the third head of the biceps brachii originating from the anteromedial surface of the humerus, below the insertion of the coraco-brachialis.

Summary

1. The pronator quadratus has an extensive origin from the dorsal border and medial and volar surfaces of the lower fourth of the ulna.

2. In addition to the usual quadrilateral muscle there is a separate triangular superficial portion overlapping the lower part of the muscle. Both parts of the muscle are well developed.

3. A muscle, the subscapulo-humeralis, in the shoulder region crosses the tendon of the subscapularis. It is not mentioned in the commoner monographs available to me.

My thanks are due to Dr Pasupati Bose, Demonstrator of Anatomy, Medical College, Calcutta, for kindly making the drawings for me.

REVIEWS

Synopsis of Surgical Anatomy. By A. L. McGregor. Second edition. (Bristol: John Wright and Sons Ltd.) 1934. Pp. xvii + 644, 639 figs. Price 17*s.* 6*d.* net.

Already this book, previously noticed in this *Journal* (vol. LXVII, p. 353), has run to a second edition. In the preface to the second edition the author remarks that he has reluctantly increased the size of the book by a few pages and that thirty-five new pages have been added. A section on palmar incisions has been added and the portion on amputations rewritten.

Précis d'Histologie: La Cellule—Les Tissus—Les Organes. Par A. Brance et J. Verne. (Paris: Masson et Cie.) 1934. Pp. 635, 420 figs. Price Broché 50 fr., Cartonné toile 65 fr.

This concise exposition of the subject of histology occupies 631 pages and uses 420 very good illustrations, most of which are signed by the artist who prepared them.

The subject-matter is divided into three sections—the cell, the tissues and the organs. Relevant biochemical and physiological data are incorporated in the text, and to each chapter there is appended a short list of monographs and recent articles related thereto. There is also an index.

The information given is accurate, includes all recent advances, is elegantly presented and easy to read.

It is a very good book, and its previous success justifies the authors in assuming that they have performed what they set out to do, viz. to prepare a book suitable for the medical student, the practitioner, and the biologist.

Entstehung und Funktion von Gefässystem und Blut auf cellular-physiologischer Grundlage. Von Dr Med. Max Hausmann. (Basel: Benno Schwabe und Co.) 1935. Lexicon-Oktav, xvi und 704 Seiten mit 192 Figuren (2 farbige Tafeln) und 15 Schemata. Preis Schweizer Fr. 56, R.M. 44.80.

This large monograph, devoted to the elucidation of the origin, function, and meaning of the vascular system and the cells circulating within it, is apparently not the work of a specialist but of a doctor engaged in a large and busy medical practice.

The book consists of three parts. The first includes a number of chapters amplifying the haemo-coelomic theory of the origin of the blood vascular system originally put forward by Lang and accepted by the present author who has furnished additional evidence in support of it. The several later chapters of this section pass in review the various classes of the invertebrates. Incidentally many other topics apposite to the main one are considered—for example, the relation of the nervous system to the organs of circulation.

The second portion of the book introduces the vertebrates by means of *Amphioxus* and concerns itself mainly with the earlier stages of the development of the coelom, mesoderm and mesenchyme and the like. There are chapters on the heart, the peripheral blood vessels, the endothelium, the reticulo-endothelial system and the red and white cells of the blood.

The third portion of the book continues with the vertebrates and is concerned mainly with the later stages of the development and physiology of the circulation. The titles of the chapters indicate such subjects as the later development of the heart, the haemopoietic organs, the physiology of the capillaries, the physiology of the heart and the central regulation of the heart.

The book concludes with a supplement on the principles of cellular physiology in the Metazoa.

There are 634 pages of text, nearly 200 figures, 15 diagrams, an index, and a register of authors' names. References are given as footnotes on the page of citation. In addition to the main subdivisions of the book the chapter numbers are followed by a concise and clear statement of their contents, so that those with familiarity of the subject can easily follow the argument of the author. In addition the reader's labour is still further lessened by a marginal heading stating the contents of the more important paragraphs.

The careful arrangement of the book, the immense mass of painstaking labour performed, the assembling of so much diverse information, the encyclopaedic usefulness of the monograph—for these we are much in the author's debt.

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